

HANDBOOK OF
PHYSIOLOGY &
BIOCHEMISTRY

ORIGINALLY "KIRKES" AND LATER "HALLIBURTON'S"

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PREFACE TO THE THIRTY-NINTH EDITION

THE continued and increasing demand for this book is indeed encouraging, but this edition cannot be expected to show the same extensive changes which distinguished the last edition from its predecessors, but many minor amendments have been incorporated and corrections made. For some years it had been realised that no textbook of Physiology of convenient size can supply all the Histology needed by a medical student, the more so as the subject is now commonly taught in relation to Anatomy. Histology had therefore been drastically reduced to sections on structure in relation to function. This reduction has provided an opportunity for extensive revision of the illustrations generally, so that the book has taken on a somewhat changed appearance. In the last two editions no fewer than eighty new illustrations have been added and for some of these I am indebted to the kindness of others. Sir E. and Lady Mellanby with Professor J. C. Brash have been good enough to provide illustrations of rickets, Professor Adrian of cerebellar localisation, Professor Gilding of metabolic rate, Sir Thomas Lewis of pain, Professor Wishart of osmotic action, Dr Broster of adrenal disease, Dr Denny Brown of changes in urinary bladder pressure, Dr Secker of intergland relationships, Dr Dawson of encephalogram, Dr Edridge-Green of colour vision, Dr Bryan Mathews of high altitude, Dr Raven of myxodœma, Dr Simpson of pituitary disease, Dr Smout and Messrs Arnold of muscle and lymph formation, and the *Journal of the American Medical Association* of thyroid diseases. The majority are, however, original but owe much to the fine draughtsmanship of Mr Staton and Mr Woods.

Unfortunately the possibility of purchase tax has made it impossible to include the usual blank pages for notes, but otherwise the needs of the medical student have been constantly kept in mind. Some teachers may think that some sections might have been omitted and others elaborated. To appease the latter, an extensive bibliography has been added so that the more enthusiastic student may readily reach more exhaustive works; but at the same time the author is of opinion from his experience of many different examinations that much of the failure of students to appreciate

points of Physiology of great practical importance is due to his being asked to learn too much at this stage. Opinion is, however, so divided as to what exactly ought to be omitted that the author feels that, in such a volume, this is best left to the discretion of individual teachers, and it will do no harm if the student catches a fleeting glance of things he need not know, for soon he will realise that his knowledge of Medicine generally must of necessity be most patchy and superficial.

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PUBLISHER'S NOTE

It may not be uninteresting briefly to recount something of the history of this book. The original author was William Senhouse Kirkes, of St Bartholomew's Hospital, and the first edition appeared in 1848; it consisted of 705 pages, and contained 97 illustrations. The title-page mentions that Dr Kirkes was assisted by Mr James Paget, who was then Lecturer on Physiology at St Bartholomew's Hospital. Dr Kirkes appears to have been a student under Mr (afterwards Sir) J. Paget, and to have been impressed with the need of making more permanent his spoken lectures, and in his preface he thanks Mr Paget for allowing him the free use of his manuscript lecture notes. The book was, for its time, one of great excellence, reflecting the clear and accurate method of exposition which always distinguished Sir James Paget's work, and *Kirkes' Physiology* rapidly became the students' favourite text-book, and new editions appeared rapidly: in these the book grew a little in size and in the number of illustrations, but showed otherwise but little change until the fourth edition came out in 1860, when Mr Savory's name appeared as editor upon the title-page. Mr (afterwards Sir William) Savory was another of St Bartholomew's worthies, and at that time was Lecturer on Comparative Anatomy and Physiology at that Hospital. With the appearance of the sixth edition (1867), Mr Morant Baker (then Demonstrator of Anatomy) was associate editor, and by this time the book was different both in matter and arrangement, so that little of the original "Kirkes" remained. Up to this time the publishers had been Taylor, Walton, & Maberly, of Gower Street. In 1869, however, the book became the property of my grandfather (seventh edition), and this edition and the next (eighth, in 1872) were not much more than reprints of the sixth edition. The ninth edition (1876), however, was completely revised, and Dr Klein, then the Lecturer on Physiology, appears to have been largely responsible for the improvement. From the tenth to the thirteenth (1892) edition, the editorship was shared between Mr Morant Baker and Dr Vincent D. Harris, his senior Demonstrator, and as successive editions appeared, the work of keeping the publication up to date fell more and more upon the shoulders of the latter.

In 1896, when a new edition was necessary, Mr Baker had died, and Dr Harris was retiring from active teaching, so my father had to look round for a new editor. Acting upon the advice of his friend, the late Sir William Gowers, he applied to Professor Halliburton, and when the latter accepted the position, the long association between the book and St Bartholomew's Hospital was severed. During the fifty-four years of this

association the book saw thirteen editions. Under Professor Halliburton's guidance, which began in 1896, the book entered upon a new era of prosperity; in twenty-nine years seventeen editions—totalling one hundred and sixteen thousand copies—were published; so, as the book had become an entirely new one, the name of Kirkes was dropped and *Halliburton's Physiology* became its recognised title.

In 1928 revision became again necessary; and as Professor Halliburton found that he needed help in preparing it, the assistance of his successor at King's College, Professor McDowall, was secured and his name added to the title.

In the thirty-fifth edition (1937) "Biochemistry" appeared on the title-page for the first time and in 1939 the thirty-sixth edition was considerably enlarged.

Since 1930 Professor McDowall has had sole responsibility for the volume, which in its present form is almost entirely his work. It is only fair, therefore, that his name should now stand alone in the place of honour on the title page, while Halliburton can be added to Kirkes as a tribute to the past editorial succession.

JOHN MURRAY.

November, 1944.

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HANDBOOK OF PHYSIOLOGY

CHAPTER I ✓

PHYSIOLOGY

THE subject of Physiology treats of the study of the phenomena occurring in all living things, but for the present purposes it is limited to the study of the activities of the animal body, especially that of man. It is part of the greater subject of Biology or the study of living things.

In making such a study we can approach the subject in a number of ways.

From Anatomy we learn the gross structure of the body, and from Histology, that is the study of its microscopic structure, we get a firmer basis from which to infer a possible function. We learn, for example, that the bodies of animals are composed of cells of great variety and that each organ has its own peculiar specialised cells arranged in a definite pattern. The appearance of the cells is often distinctive and may tell us whether they are protective, secretory, nervous or connective.

By a chemical study of the tissues and of the various substances found in living things and of those taken into them, we are able to relate to each other the various chemical processes which take place as they might be carried out in a chemical laboratory. This constitutes Biochemistry. From it we learn how the body breaks down the various substances found in nature, makes use of them, and returns to its environment those it does not need or has used.

By a study of the movements and other physical processes which take place in the body (Biophysics) we understand the mechanics and dynamics of the body. From this we understand, for example, how the blood circulates and how air is sucked into the lungs.

Physical Chemistry, too, adds its quota and indicates such things as the principles by which substances may pass through the various membranes of the body especially those of the cells themselves.

In Biology we trace the structural functions of organs of lower

animals and how they have been evolved, and we see how, as we go down the animal scale, the processes become simpler and simpler until all the more essential ones are performed by a single cell, a cell which is alive and capable of reproducing itself. There we find ourselves up against the problem of life itself which so far has defied complete analysis, but by the study of Physiology from its various angles we find out many of the factors on which it depends and how we can do much to assist in its prolongation and to add to its happiness, which is the function of Medicine.

CHAPTER II ✓

THE STRUCTURE AND CHARACTERISTICS OF LIVING THINGS

The Structure of Living Things.—All living things are composed of minute cells the form of which can be seen with the aid of a microscope. They are at first unicellular and the simplest, such as the amoeba, remain so, but all the larger animals rapidly become multicellular and amongst its various cells there is a division of labour (so to speak), different cells having different function but all being co-ordinated for the benefit of the animal as a whole.

The essential and peculiar constituent of cell structure is the jelly-like substance *protoplasm* which is largely protein in nature, but does not remain alive unless it is associated with at least the chlorides of sodium, calcium, and potassium in solution in water. If a cell is placed in a solution in which any one is absent, or not in its proper proportion, it rapidly dies, but if properly kept it will not only live but multiply. For more prolonged activity a great variety of other substances are probably necessary in minute amounts. There is some argument as to the nature of protoplasmic structure. Certainly when treated so as to stain or preserve it a fibrillar network is seen, and this has been seen in untreated specimens of white blood corpuscles which are singularly like amoebæ in their appearance and activities.

Controlling the activities of every living cell is a *nucleus* which stains more deeply than the rest of the cell, and the nucleus may show a nucleolus. The function of the various parts is unknown, but the chemical composition of nuclei has been shown to be quite different from the rest (cytoplasm) of the cell. Some cells have more than one nucleus.

All animal cells also have an "attraction sphere" which is prominent in actively dividing cells, a fact which suggests its importance in the process of cell division.

The Functional Characteristics of Living Things.—Life has been described as resting on a tripod of security, nourishment, and reproduction. On the first two depends the life of the individual, on the third the continuance of the species. Living things, therefore, show signs of activity. Of these the one most universally

demonstrable is that of *assimilation*. It takes food with which to build its body, and to be transformed into mechanical energy, and it takes in oxygen. This latter activity is usually the most easily shown sign of life. By studying oxygen-intake we can discover whether a man or an amoeba is alive.

Living things also have the power of *excretion*, that is, of getting rid of the waste products of its bodily activities. They have the power of growth and of reproduction. Growth is really the characteristic of living things, for machines such as engines do, in a sense, assimilate and excrete. The *growth* of a living thing is not, however, like that of crystals by addition but by the multiplication of its existing elements and intake into its substance. Even when a tissue has ceased to grow in the ordinary sense it still has to repair itself, for there is a considerable amount of wear and tear associated with living. Actually the individual cells of the body are constantly dying and being replaced. Living material is, therefore, never in a static condition, but is also undergoing intramolecular rearrangements the total sum of which is called metabolism.

Many cells show the power of *irritability*, that is, the power of responding to an external agent or stimulus. Commonly such a stimulus produces observable movement. Movement, however, merely indicates that only the part concerned is alive and retains its irritability. The muscles of a frog, for example, remain alive and capable of contracting several days after the animal from which it has been removed is dead. Death, therefore, may be said to occur when the animal as a whole has ceased to assimilate.

The Relation of the Cell to its External Environment.

The simplest animal organism, consisting of a single cell, is in immediate contact with its environment water, from which it receives its nutrient material and oxygen and to which it returns its waste materials. Even in the most complex animal each cell leads a similar life in immediate contact with the tissue fluid in which it is bathed. Only certain cells come into immediate contact with the external environment, the other cells of the body all benefiting indirectly through this contact but this local environment, so to speak, is brought into contact with the external environment in which the animal lives by means of the blood supply. For example, some of the cells of the respiratory tract are adapted for the passage of oxygen, while certain cells of the digestive tract permit the intake of nutrient materials. The oxygen and nourishment from the environment are transported by way of the

specialised cells to every other cell in the body. This transport is accomplished by the circulation of the blood.

The Interrelationship of Structure and Function of Individual Tissues.

The microscopic appearances of organs and tissues concern the subject of Histology, but here it may be indicated how individual tissues play their part. It should, however, be pointed out that although heredity and evolution are important in the development of the structure of an organ, its activity is equally so as the individual tissues grow or degenerate according to the use to which they are put. We are familiar with the increase of muscle of the arms and thickening of the skin of the hands which occurs as the result of hard manual labour, and also with the effects of training generally. If we consider animals generally we see an evolution of both structure and function; a convenient example of this is seen in the evolution of the nervous system which is considered later.

The Functions of the Epithelial Tissues.

All free surfaces are covered by one or more layers of simple cells which are adapted to the needs of the part.

Stratified epithelium, which covers the exposed part of the body and constitutes the outer layer of the skin, is many cells thick. The outer layers become squamous, flattened, and may be horny, and eventually are shed as scales. Where there is any special irritation the outer layers are much thickened as on the palms of the hands or the soles of the feet. This may occur also after more obvious injury to the skin, which is essentially the protective epithelium of the body.

Pavement epithelium (endothelium) covers less exposed parts. In general, it lines many of the body cavities, including the blood- and lymph-vascular system, the alveoli of the lungs, the serous cavities (pleuræ, pericardium, and peritoneum), and also the synovial cavities of the joints. The cells are flat and permit free passage to gases and fluids, in the case of the lung alveoli, interchange of gases occurs and in the serous cavities free movement of the lungs, heart, and abdominal viscera is obtained through the lubricating action of the fluid (lymph). It is only a single layer thick.

Transitional epithelium is an intermediate variety which is only a few layers thick and only becomes flattened on its surface. It is found only in the urinary tract where it protects against the hæmical substances of the urine and probably prevents reabsorption.

Columnar epithelium is a more active type of epithelium. It

manufactures special substances from the blood which we know as secretions and it has selective powers controlling absorption into the blood. It does both as it covers the mucous membrane or lining of the alimentary canal and some of the tubules of the kidney. Most glands are infoldings from such columnar epithelial surfaces, and wherever such tissue is seen it can be assumed that it has these functions.

Ciliated Epithelium.

The ciliated cell is usually columnar in shape and surmounted by a bunch of fine tapering filaments which were originally called cilia because of their resemblance to eyelashes.

In the larger ciliated cells, the border on which the cilia are set is bright and composed of little knobs, to each of which a cilium is attached; in some cases the knobs are prolonged into the cell protoplasm as filaments or rootlets (fig. 1). The bunch of cilia is homologous with the striated border of columnar cells.

The function of the cilia is to cause a movement of substances or objects along the surfaces they line. For example, cilia line the air passages (but not the alveoli) and they cause a current of mucus and entangled dust to move towards the throat (fig. 2). In the Fallopian tubes and upper part of the uterus

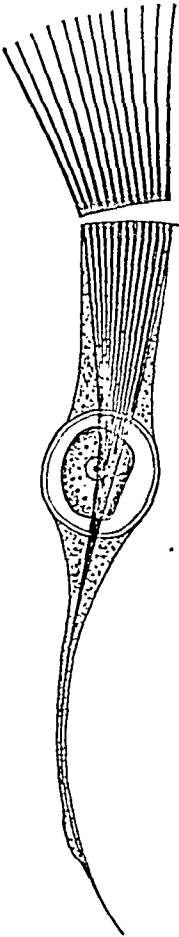


FIG. 1.—Ciliated cell from the intestine of a mollusc. (Engelmann.)

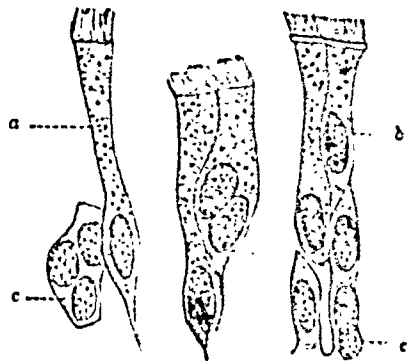


FIG. 2.—Ciliated epithelium from the human trachea. a, Large fully-formed cell; b, shorter cell; c, developing cells with more than one nucleus. (Cadat.)

they assist the movements of ova, and in the ducts of the testes those of the spermatozoa. The tail of a spermatozoon may itself be

regarded as a cilium; some protozoa also move by means of cilia. Cilia are found also in the ventricles of the brain and in the central canal of the spinal cord; in the gills of marine animals, and in the gullet of the frog.

Ciliary motion may conveniently be studied in the latter, or in the gill of a mussel kept moist by a 0.6 per cent. saline. It may be observed under the microscope and, in the case of the frog, the movements of minute pieces of carbon may be studied.

The cilia are seen to be in constant rapid motion, each cilium being fixed at one end, and swinging or lashing to and fro. The general impression given to the eye of the observer is very similar to that produced by waves in a field of corn, and the result of their movement is to produce a continuous current in a definite direction, and this direction is always the same on the same surface, being usually in the case of a cavity towards the external orifice.

The exact explanation of ciliary movement is not known; whatever may be the precise cause, the movement must depend on some changes going on in the cell to which the cilia are attached, for, when the latter are cut off from the cell, the movement ceases, and when severed so that portions of the cilia are left attached to the cell, the attached and not the severed portions continue the movement.

It would seem most likely that the movement is essentially similar to that which takes place in amœbæ or white blood corpuscles which throw out processes, and that changes in the tension of the fluid in the cilia cause them to straighten and bend.

The Effect of some External Agents on Amœboid and Ciliary Movements.

Although the movements of amœboid and ciliated cells may be loosely described as spontaneous, yet they are produced and increased under the action of external agencies which excite or stimulate them.

Ciliary and amœboid movements are increased by small rises in temperature and by dilute alkalis. Additional movement increases the demand for oxygen (Gray). Lack of oxygen causes cessation of ciliary movement. So also does cold, a fact which may be important in the inception of the common cold. Temperatures above 45° C., acids, strong alkalis and anaesthetics have a similar effect.

More detailed information on the subject is to be found in the writings of Gray and of Negus.

The Functions of the Connective Tissues.

In these tissues, in addition to the cells, there exist fibres which act mechanically for the support and protection of tissue, and in many cases the fibres so predominate that the cells are scarcely seen. It is a matter of debate whether the fibres are altered cells or are deposited in the intercellular substance.

Fibrous tissue is a typical holding or connective tissue and its characteristic is that it does not stretch. It consists of bundles of white fibres. It forms, therefore, the tendons of muscles, the sacs of joints, part of the pericardial sac of the heart, and innumerable sheets of fibrous tissue or fascia to which muscles are attached or bones held together. Fibrous tissue is formed in wounds after injury, and since it tends to shrink often causes unsightly contractions in scars. If, however, it is subjected to sustained tension it will stretch. The fibres are composed of the protein material collagen which is converted into gelatin by boiling. For this reason we boil or stew the meat of an old animal which tends to be fibrous or tough. The activity of the fibroblasts or cells which form the tissue appears to require the presence of vitamin C in the diet.

Elastic tissue has fewer fibres which are yellow in colour, and which, as their name suggests, give elasticity to the part. Elastic fibres are found in blood vessels where they appear to be joined together as membranes. They are frequent in the lungs and they assist in holding together and in giving elasticity to the cartilages of the trachea and bronchi. They are well seen in the ligamentum nuchæ connecting the skull to the vertebral column.

Areolar tissue is the name given to the loose connective tissue which contains not only fibres of both kinds but cells. The cells are of several varieties. The *fibroblasts* in connection with which the fibres of the tissue are developed. The *histiocytes* which are characterised by their taking up vital dyes, that is, dyes injected in a living animal; they are probably part of the reticulo-endothelial, macrophage or scavenging, system of the body. There are also cells which may be granular, the *mast cells*, or non-granular, the *plasma cells*, which are very like the basophil white cells and the lymphocytes of the blood. They probably have the function of dealing with bacteria which may gain access to the tissue. *Pigment cells* are also sometimes seen.

In addition, areolar tissue stores fat in large vesicular fat cells which, when excessive, cause it to be known as **adipose tissue**. It is also in the areolar tissue that water is extensively stored. This may be stored not only as free fluid but apparently also within the fibroblastic cells which may become quite swollen.

The other tissues are dealt with more appropriately in relation to the systems of which they form a predominant part.

THE GENERAL FUNCTIONAL DESIGN OF THE HIGHER ANIMAL BODY.

As we have said, all living things have activities, but by far their most important is that of keeping themselves alive by feeding and protecting themselves. This, all the more elaborate animals do by means of their voluntary muscles which are under the control of the brain.

The voluntary muscles, which we shall discuss in detail later, are structures which, by contracting, perform mechanical work, and in doing so transform chemical into mechanical energy with the evolution of heat. They act like engines and use what is essentially the same fuel as the internal combustion engine of a motor-car, namely, carbon and hydrogen which are transformed into carbon dioxide and water. Carbon and hydrogen are the essential constituents of the hydrocarbon, petrol, and also of the carbohydrate, glucose, which is used by the body.

These substances are supplied to the muscle by an artery which carries the carbon, hydrogen, and oxygen, a combustion mixture analogous to that supplied by the carburettor to the engine of a motor-car. The exhaust, which is chiefly carbon dioxide and water, is taken away by the veins.

Now the substances necessary for the engine, *i.e.* the fuel and the oxygen, have to be supplied from the outside world. The blood in the artery has been previously pumped to the lungs which, we have already noted, are specialised organs in contact with the outside world, via the windpipe, while the nourishment is picked up by that portion of the blood which passes to the digestive tract which is in continuity with the external environment at the mouth. As we shall see later, the detailed structure of the lungs and the alimentary canal are such that the blood is spread out very thinly on an enormous surface, much larger than the total skin surface of the body and so it takes up what it needs very rapidly.

The extent to which the muscles need oxygen determines the rate at which it is supplied, for the carbon dioxide produced increases the respiratory movements while when more blood reaches the heart it increases automatically its output.

The substances of the exhaust from the engine, carbon dioxide, and water, are likewise transported to the lungs, skin, and kidney by which they are returned to the outside world.

A cycle is completed by the plants which under the influence of sunlight transform the carbon dioxide and water back into carbohydrate, the chief nourishment of animals.

In this description of the body the heart and lungs appear as the servants of the muscles and it is an important fact in curative medicine that physical and mental rest put the whole body at rest.

So far many substances which we need for nourishment have not been mentioned. They correspond to the materials of which the engine is made and need only be supplied in very minute amounts. In the case of the body the most important substance concerned is protein which is the essential chemical component of all living things. Its detailed composition is discussed later, but here it may be said that amongst its essential constituents are nitrogen and sulphur. The chemical changes which take place in the various substances in the body are known as Metabolism.

The muscles are also in contact with the external environment by means of the nervous system, and here we may contemplate how many of our movements are the result of stimuli from the outside world. Such stimuli usually determine at least the exact time at which the movements are made, through, of course, the intervention of the brain.

The study of muscular movement may be considered to be a suitable point at which to commence the study of Human Physiology, for what has been said of the muscle applies to every cell and tissue of the body, but, with the exception of the heart, none are more active than the voluntary muscles and none make such demands on the organism as a whole.

The term organ is a loose anatomical one and is applied to structures which can be conveniently separated by dissection. Commonly, however, they have a well recognisable characteristic microscopical structure and function.

In performing the bodily functions the organs themselves are arranged in groups which are, by convention, known as **systems**. Thus the respiratory system includes all structures and processes which are concerned with the uptake of oxygen and elimination of carbon dioxide, but there are really no hard and fast boundaries to any system as they all work together for the benefit of the whole body.

Popular lectures on the body as an engine have been given by A. Keith and A. V. Hill.

CHAPTER III

MUSCLE

THE most important movements of the higher animals are brought about by muscles which possess the power of contraction or shortening, usually as a result of impulses conveyed to them by nerves.

The majority of the muscles of the body are attached to bones which act as levers. Thus: when we want to bend the elbow, impulses from the brain descend by way of the spinal cord and nerves to muscles which are attached to the bones of the lower arm at one end and to the bones of the upper arm or shoulder girdle at the other. Since the bones of the lower and upper arms are hinged at the elbow, contraction of the muscles causes a bending of the elbow. The study of the movements of muscles and their effect on the bones is now dealt with by the anatomists, and need not be entered into here. In some instances muscular tissue pervades or surrounds cavities, and its contraction causes movement of the contents as in the case of the digestive tract.

The Skeleton.

This is the framework of bone on and in which the body is built. Its detailed study concerns anatomy, while its physiological aspects are postponed until the student is familiar with the general processes on which its formation depends.

Muscular Tissue.

Muscle is popularly known as flesh. The muscles may be divided from a physiological standpoint into two classes—the *voluntary* muscles, which are under the control of the will, and the *involuntary* muscles, which are not. All muscular tissue, whether under the will or not, is controlled by means of the nervous system. The involuntary muscles are controlled by a specialised part of the nervous system.

When muscular tissue is examined under the microscope, it is seen to be made up of small, elongated, thread-like cells, which are called *muscle-fibres* and which are bound into bundles by connective

tissue. In involuntary muscles there is a certain amount of cement substance, stainable by nitrate of silver, between the fibres.

There are three varieties of muscle-fibres: (1) striated muscle-fibres, which occur in the voluntary muscles; (2) unstriated muscle-fibres which bring about movement in the internal organs; and (3) cardiac or heart muscle-fibres, which are striated like (1), but are otherwise different. Their other differences are summarised later (p. 51).

Voluntary or Striped Muscle.

Voluntary muscles are sometimes called *skeletal*, and they constitute the whole of the muscular apparatus attached to the bones.*

The fibres vary considerably in thickness and length, but they average $\frac{1}{500}$ inch in diameter, and are about 1 inch in length. Each fibre is cylindrical in shape and has rounded ends; many become prolonged into tendon bundles by which muscle is attached to bone.

Each fibre consists of a sheath, called the *sarcolemma*, which encloses a soft material called the *contractile substance*.

The contractile substance within the sheath is made up of alternate stripes of dark and light substance which give voluntary muscle its characteristic appearance. Huxley succeeded in making casts of muscle-fibres in collodion films and showed that the light and dark stripes appear on the casts. He therefore concluded that the striped appearance was

due to optical phenomena. The stripes also stain differently, so presumably differ in chemical composition.

Muscle-fibres contain oval nuclei. In mammalian muscle these are situated just beneath the sarcolemma; but in frog's muscle they occur also in the thickness of the muscle-fibre.

A muscle-fibre is made up of *fibrils* or *sarcostyles*, which are held together by a network known as the *sarcoplasm* (represented as white lines in fig. 3). By the use of certain reagents, such as osmic acid or alcohol, the fibrils may be completely separated from one another.

The rapidity of muscular contraction seems to be proportional to the clearness of the cross-striation, and insects' muscles which are remarkable for perfection of mechanism have consequently been the subject of many researches. In the wing muscles the sarcostyles are separated by a considerable quantity of interstitial sarcoplasm,

* The muscle-fibres of the pharynx, of part of the œsophagus, and of the middle and the external ear, though not under the control of the will, have the same structure as voluntary muscle-fibres.

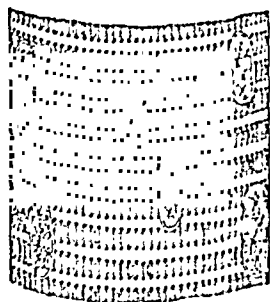


FIG. 8.—Muscle-fibre of a mammal highly magnified. The surface of the fibre is accurately focussed. (Schafer.)

which may be of nutritive importance, and according to some observers possesses a certain amount of contractility; at any rate it allows the intimate structure of the individual sarcostyles to be worked out thoroughly, and Sharpey Schafer has arrived at the following conclusions:—

Each sarcostyle is subdivided, by a transverse line (Krause's membrane*) in the middle of each light stripe, into successive portions which are termed *sarcomeres*. In each sarcomere is one dark stripe or *sarcous element*. The sarcous element is really in two sections which, in the stretched sarcostyle (fig. 4, B), separate

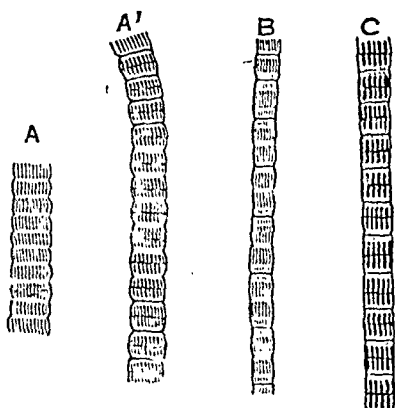


FIG. 4.—Sarcostyles from the wing-muscles of a wasp.

- A A', Sarcostyles showing degrees of contraction.
 B, A sarcostyle extended with the sarcous elements separated into two parts.
 C, Sarcostyles moderately extended (semidiagrammatic). (E. S. Schafer.)

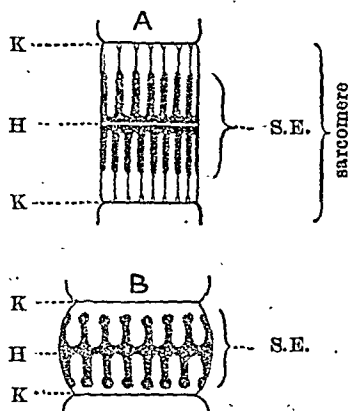


FIG. 5.—Diagram of a sarcomere in a moderately extended condition, A, and in a contracted condition, B.

- K, K, Krause's membranes; H, plane of Hensen; S.E., poriferous sarcous element. (E. S. Schafer.)

at the line of Hensen. Between each end of the sarcous element and Krause's membrane lies a clear interval which is more evident in the extended sarcomere (fig. 4, B), and which diminishes on contraction (fig. 4, A). The sarcous element is pervaded with longitudinal canals or pores which are open towards Krause's membrane and closed at Hensen's line. As the sarcostyle contracts, a large proportion of the clear part of the sarcomere passes into these pores and disappears into the sarcous element which swells up and becomes wider, with a consequent shortening of the sarcomere (fig. 5, B). As the sarcostyle is extended the clear substance passes out from the pores of the sarcous element and lies between it and Krause's membrane. There is a compensating lengthening and narrowing of the sarcomere (fig. 5, A). It should be noted that the sarcous element does not

* Also called Dobie's line. The membrane is probably an optical phenomenon for Kühne discovered that a threadworm could crawl through it without difficulty and without destroying it.

lie free in the middle of the sarcomere, but is attached at the sides to a fine enclosing envelope, and at either end to Krause's membrane by fine lines running through the clear substance (fig. 5, A).

These conclusions are interesting, because they bring into harmony amoeboid, ciliary, and muscular movement. In all three instances we

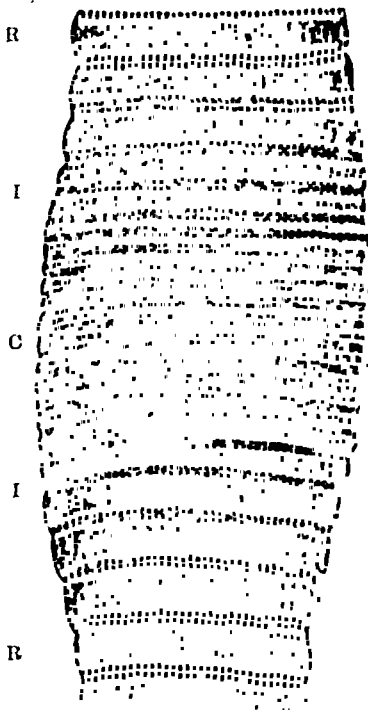


FIG. 6.—Wave of contraction passing over a muscle-fibre of water-beetle. R, R, Portions of the fibre at rest; C, contracted part; I, I, intermediate condition. (Schafer.)

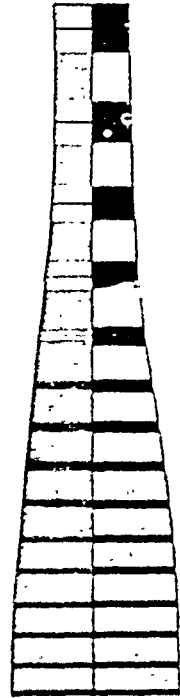


FIG. 7.—This figure (after Engelmann) illustrates the appearance of a muscle-fibre as examined in ordinary light (left-hand side) and in polarised light (right-hand side). In the upper part of the diagram the fibre is not contracted. The dark bands are seen to be bright by polarised light, owing to their being largely made up of doubly-refracting sarcous elements; during contraction, fluid passes from the singly-refracting or isotropous light band into the doubly-refracting dark band, which, in consequence, becomes widened out.

have protoplasm composed of two materials, spongioplasm and hyaloplasm. In amoeboid movement the irregular arrangement of the spongioplasm allows the hyaloplasm to flow in and out of it in any direction. In ciliary movement the flow is limited by the arrangement of the spongioplasm to one direction; hence the limitation of the movement in one direction (see pp. 11-12). In muscle, the definite arrangement of the spongioplasm (represented by the sarcous element) in a longitudinal direction limits the movement of the hyaloplasm

(represented by the clear substance of the light stripe), so that it must flow either in or out in a particular direction. The contraction of a whole muscle is the sum total of the contraction of all the constituent sarcomeres.

Red and Pale Voluntary Muscles.

In most animals some of the muscles are pale and some white because of the amount of *hæmoglobin* and fat they contain. The red muscles have thinner fibres, more sarcoplasm, more marked longitudinal striation, but less marked transverse striations and contract more slowly.

The study of their distribution in different animals has shown that the red fibres are particularly concerned with sustained activity. They are, for example, particularly prevalent in the pectoral muscles of soaring birds but not in ordinary domestic birds. In man the red fibres predominate in the soleus and pale in the gastrocnemius but most muscles are more mixed. We shall see later that the red muscles are particularly concerned in the more sustained reactions for the maintenance of posture and equilibrium. Denny-Brown, to whom we owe these facts, has shown that red muscles go into tetanus at the surprisingly low rate of 5 to 8 stimuli per second.

CHAPTER IV

EXCITABILITY AND STIMULATION

Excitability or **Irritability** is the power which certain tissues possess of responding by some change (transformation of energy) to the action of an external agent which, whatever its nature, we call the **stimulus**.

The nature of the response depends on the nature of the tissue. Some tissues move, some secrete, some discharge electricity, *e.g.* the electric organs of some fishes.

Excitable tissues may be stimulated by mechanical or chemical agencies. They may also be stimulated by suitable electrical stimuli, and in the study of excitability the latter stimuli are generally used as they do not damage the tissue and are easily controlled. The tissues in the body are stimulated by nervous impulses. We can see the response to such stimulation in the nerve to a muscle of a frog. It may be stimulated by a tap or pinch, by a chemical agent (acid or salt), by a direct or an induced current, and normally by the nervous impulses which reach it from the nerve centres. When we make a voluntary movement, we cause a nervous impulse to pass down an excitable nerve to an excitable muscle. Some tissues are specially excitable to certain kinds of stimuli rather than to others. For example, unstriated muscle is most easily stimulated by stretching. Glycerol stimulates nerve but not muscle directly; while ammonia stimulates muscle but not nerve.

We may regard stimuli as liberators of energy; muscle and nerve and other irritable structures undergo disturbances in consequence of a stimulus. The disturbance is some form of movement—visible movement in muscle, molecular movement in nerve. A stimulus may be regarded as added motion. Gowers compared it to the blow that causes dynamite to explode, or the match applied to a train of gunpowder. A very slight blow will explode a large quantity of dynamite; a very small spark will fire a long train of gunpowder. So in muscle or nerve the effect is often out of all proportion to the strength of the stimulus; a light touch on the surface of the body may elicit very forcible nervous and muscular disturbances; and, moreover, the effect of the stimulus is propagated along the nerve or muscle without loss.

Electrical Stimulation.

Stimulation of an excitable tissue may, as we have seen above, be brought about chemically or mechanically, but most conveniently by an electric current from a cell or a battery supplying 1-2 volts. This method has the great advantage that within limits it does not damage the tissue and may be repeated many times. It is not necessary to describe in detail the electrical apparatus.



FIG. 8.—Diagram of simple electrical circuit which is completed when the tissue to be stimulated is placed across the electrodes E.

Wires from the positive and negative poles, of the cell form the electrodes, the former being known as the anode and the latter as the cathode. With a direct current stimulation occurs only at the "make," but not when the current is "flowing." Actually, the passage of an electric current through a nerve causes it to be temporarily inexcitable in the region of the anode, where it produces a state known as anelectrotonus.

If the nerve or muscle is laid across the electrodes, the electrical circuit is completed and stimulation occurs. The experiment can, however, be more conveniently carried out by first laying the nerve across the electrodes, and making and breaking the circuit by means of a key (fig. 8).

In many experiments it is desirable to vary the strength of stimulation, and this can be done most conveniently by using an induced current from a transformer or induction coil. The two circuits are shown in fig. 9. It is seen that each circuit is quite

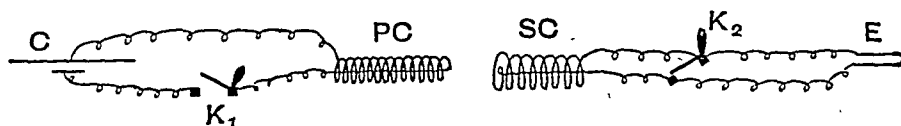


FIG. 9.—Circuit to give induced currents. C—cell: PC—primary coil: SC—secondary coil: E—electrodes: K₁ and K₂—keys in the primary and secondary circuits respectively. Note that K₂ short-circuits the electrodes.

separate from the other, and it may readily be shown that a current only passes in the secondary circuit when an alteration is made in the strength of the primary. A current is obtained in the secondary *only* at the "making" (closing of the key) and "breaking" (opening of the key) of the primary circuit. The nearer the primary and secondary coils are to one another the stronger is the induced current in the secondary circuit. The strength of the stimulating current can therefore be varied by varying the distance between the two coils. It must be understood that there is no fundamental qualitative difference between a direct and an induced current. The

essential differences are the short duration and the change of direction of the induced current which occurs at each make and break.

It will be observed that a short-circuiting key is used in the secondary circuit. A simple key would not be so effective because of the phenomenon of unipolar induction.

The "break" effects are stronger than the make effects; this is easily proved by placing the electrodes on the tongue and is due to Faraday's extra current. This current is produced in the primary coil by the inductive influence of contiguous turns of its wire on each other; its direction is against that of the battery current at make, and so the make shock is lessened. At the break the extra current is of such short duration (because when the circuit is broken there can be no current at all) that for all practical purposes it may be considered as non-existent.

For many physiological purposes an automatic interrupter (Wagner's hammer), on the principle of an ordinary electric bell, is introduced into the primary circuit and is attached to the end of the induction coil. It may have a device for equalising the make and break currents. By the use of such an interrupter it is possible to set up nerve impulses in nerves at rates approximating those which occur normally.

There is a maximal rate of stimulation of all tissues and if a current is alternated extremely rapidly it does not stimulate at all because it has not time to set up a sufficient movement of ions. For example, ordinary house current of 250 volts alternating at 50 cycles is lethal to the heart, but not so if it alternates at over 100,000 per second, although such a current will light an ordinary electric bulb.

Fortunately the body is normally protected by skin which when dry has a resistance of the order of 50,000 ohms, but this is greatly reduced if the skin is wet.

Measurement of Excitability.

Tissues exhibit considerable differences in excitability to different kinds of currents. Smooth muscle, for example, will respond to stimulation by a direct current, but not to an induced current (see p. 17). There is no fundamental qualitative difference between these two currents. They are merely of different strengths and last for different times, the induced current being stronger but of very short duration. Speaking generally, it has been found that the shorter the period of stimulation the stronger must be the current which will produce an effect and *vice versa*. It has also been shown that each tissue may be stimulated by a certain strength and duration of electrical stimulation which cannot be varied beyond certain limits. It is for such reasons that a current of 10,000 volts

if very rapidly alternating may not cause death, although a shock of 500 volts from the live wire or rail of an electric train may be fatal.

Our knowledge of this subject we owe largely to Keith Lucas of Cambridge, and later to Lapicque, of Paris, and their co-workers. The latter introduced the following terms for the measurement of excitability:—

Rheobase is the intensity in volts of the weakest constant current which, if continued indefinitely, will excite.

Chronaxie is the minimum time required for excitation by a current of twice the intensity of the rheobase.

Rheobase is determined with a battery, voltmeter, and variable resistance; for chronaxie some method of stimulating for very short periods is needed. A heavy pendulum or spring which knocks over a make key and a fraction of a second later breaks the circuit (Keith Lucas) may be used, but the discharge of a condenser is also employed. The rheobase for the cut sciatic of the frog is 0.2 to 0.3 volt, and the chronaxie is 0.3 to 0.4 thousandths of a second.

Chronaxie varies widely in different nerves even in the same animal. In general it is least in rapidly contracting muscles supplied by large nerve-fibres. Differences are also noticeable in nerves treated by various reagents: those which swell the myelin sheath for instance increase the rheobase and shorten the chronaxie. In man, Bourguignon found that the extensors have a chronaxie of 0.1σ ($\sigma = .001$ sec.) while that of the flexors is 0.4σ or more. The relation of these data to the activity of the central nervous system has not been as yet fully studied. Cutting a nerve roughly doubles the chronaxie it possesses in the intact state.

Difference in excitability explains why degenerated muscle fails to respond to faradic stimulation yet responds to a galvanic stimulus, also why different results may be obtained when a mixed nerve is stimulated by different currents. In the latter instance it may be assumed that the nerve-fibres which compose the nerve have different chronaxies. It is also claimed that fatigued or curarised* muscles have an altered chronaxie and cannot be stimulated by impulses which pass down their nerves. (See Fatigue.)

Refractory Phase.—After a tissue, such as a muscle or a nerve, has been excited by a stimulus it is refractory for a short space of time: that is, it fails to respond to a stimulus. In ordinary muscle and nerve this refractory phase is very short, but in cardiac muscle it lasts throughout the duration of the contraction. The refractory phase is of importance since it gives time in which a tissue may recover its power of activity.

* The drug, curari, is a South American arrow poison.

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CHAPTER V

THE CONTRACTION OF MUSCLE

NORMALLY the voluntary muscles contract as a result of nervous impulses reaching them from the central nervous system by way of their nerves. We can, however, set up a nervous impulse in a nerve artificially and so cause the muscle to contract. For this purpose we generally use a **nerve-muscle preparation**, gastrocnemius or calf muscle and sciatic nerve of a frog, the muscles and nerves of which live for a long time after removal from the body. Strips of muscle may, however, be substituted.

Muscle undergoes the following changes when it contracts:—

1. Changes in form.
2. Changes in extensibility and elasticity.
3. Changes in temperature.
4. Changes in electrical condition.
5. Chemical changes.

Changes in Form.

The Myograph.—There are many different forms of this apparatus, which was originally invented by Ludwig and Helmholtz to record muscular contraction.

In each type the bony origin of the gastrocnemius is held firmly, usually by a pin through the knee-joint, while the tendo Achillis is tied to a weighted lever the end of which bears a writing-point such as a piece of parchment paper (fig. 10). This records the magnified contractions of the muscle on smoked paper which is wrapped round a cylinder. When the cylinder is stationary the upstroke and downstroke of the writing-point fall on the same part of the surface; but if the cylinder is rotating a muscle curve or myogram is obtained. If a permanent record be desired the paper may be removed from the cylinder, and the soot fixed by passing the paper through a solution of resin in spirit and allowing it to dry. The screw on which the lever rests can be adjusted so that the lever rests on it till the muscle contracts; the muscle therefore does not take the weight until contraction has begun (*after-loading*). The spindle of the rotating cylinder bears two metal arms which can

be brought together to form one arm if desired. The free end of each arm can be made to press over at one point in the drum's revolution a key which lies in the primary circuit of the inductorium; thus the muscle can be made to contract once or twice for each revolution. The secondary coil should be pulled out until the muscle is stimulated by the break shock only. To find the exact point of stimulation, the drum is moved round by hand until the contact in the primary circuit is just broken.

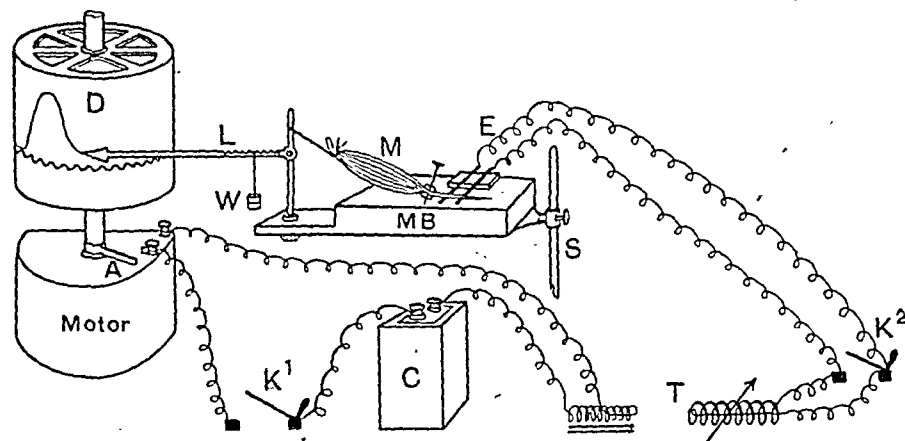


FIG. 10.—Apparatus for recording muscle contraction. The gastrocnemius muscle *M* is fastened to the board *MB* by means of a pin through the knee-joint and its Achillis tendon attached to the lever *L*, which writes on the smoked drum *D*. The lever may be weighted by *W*. Stimulating current is supplied by the cell *C*. When the key *K*¹ is closed or opened a current is induced by means of the transformer *T* in the secondary circuit supplying the electrodes *E* which applied to the sciatic nerve supply the muscle. The strength of the current can be varied by altering the distance between the coils of the transformer. The key *K*² is introduced to short circuit the electrodes when desired.

To keep the preparation fresh during an experiment, it must be moistened with **normal saline** (0.65 per cent. NaCl in water for frog's muscle, this being the concentration of salts in the fluid which normally bathes it), or it may be kept in a moist chamber, *i.e.*, a chamber in which the air is kept saturated with moisture.

The events recorded in the myogram can be timed. The simplest time-marker is a tuning-fork vibrating 100 times a second. This is struck, and by means of a writing-point fixed on to one of the prongs of the fork, these vibrations may be written beneath the myogram. More elaborate forms of electrical time-markers are frequently employed.

The Simple Muscle Curve.—One of these is shown in fig. 11. The muscle was stimulated by a single induction-shock, at the instant marked *P* on the base-line.

It will be observed that after the stimulus has been applied there is an interval before the contraction begins. This interval is called the **latent period**, and when measured by the tuning-fork

tracing is seen to be about $\frac{1}{100}$ sec. During the latent period there is no *visible* change in the muscle.

The second part is the **stage of contraction** proper. The lever is raised by the shortening of the muscle. The contraction is at first very rapid, but then progresses more slowly to its maximum.

The next stage is the **stage of relaxation**. After reaching its highest point, the lever descends in consequence of the elongation of the muscle. The small waves which follow the main curve are due for the most part to the recording apparatus, and are most marked when the contraction is rapid and vigorous.

With regard to the latent period, it should be pointed out that if the muscle is stimulated indirectly, *i.e.* through its nerve, some of the apparent lost time is occupied in the propagation of the nervous

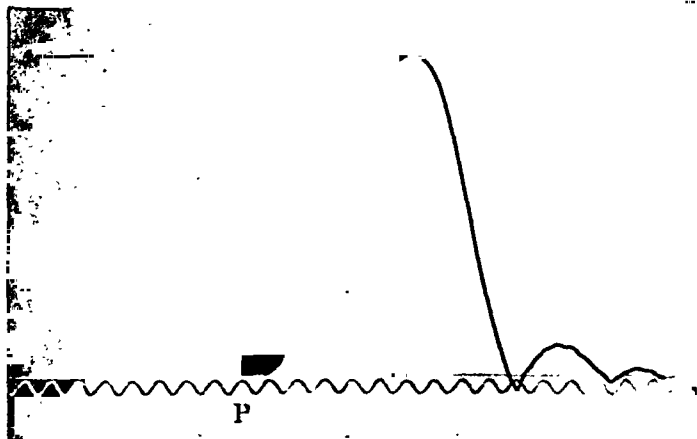


FIG. 11.—Simple muscle curve.

impulse along the nerve and across the end plate to the muscle. To obtain the true latent period, this must be deducted. Then there is latency in the apparatus. It must be understood that with the ordinary class apparatus results are only approximate. Errors arise from inertia and friction of the lever. These errors may be excluded by photographing the contracting muscle on a sensitive photographic plate travelling at an accurately timed rate or by the use of the isometric method (see p. 30). By such means it is found that the true latent period is much shorter than was formerly supposed. It is only $\frac{1}{500}$ of a second or less.

Actually a simple twitch contraction of a frog's muscle takes only 0.06 sec. and relaxation 0.13 sec. A mammalian twitch is about 3 times faster. Such results show the importance of the apparatus in experimentation.

Factors modifying the Character of the Curve.

1. *Influence of strength of stimulus.*—A minimal* stimulus is that which is just strong enough to produce a contraction. If the strength of stimulus is increased the amount of contraction as measured by the height of the curve is increased, until a certain point is reached (maximal stimulus), beyond which increase in the stimulus produces no increase in the amount of contraction. This is because the stronger the stimulus, the more muscle-fibres are thrown into action and when all the fibres are stimulated the maximum is reached. This is not to be confused with the phenomenon known as the beneficial effect of contraction (see below). In this way a muscle grades its contraction for it has been observed microscopically by sprinkling finely divided mercury on the muscle that if an individual fibre contracts at all it contracts to a maximum. This is known as the *all or none* phenomenon, which is discussed later in relation to cardiac muscle which acts like a single fibre.

2. *Influence of load.*—Increase of load within certain limits (see p. 31), applied by weighting the lever, decreases the amount of contraction, until the muscle is unable to lift it.

3. *Effect of temperature.*—Cold at first increases the height of contraction, then diminishes it; otherwise the effect is very like that of fatigue, increasing the duration of all stages of the curve.

Moderate warmth increases the height and diminishes the duration of all stages of the curve, latent period included. This may be shown by dropping salt solution at different temperatures on to the muscle before taking its curve (fig. 12). It must, however, be understood that the increased height during the application of heat is caused mainly by the mechanical effect of the increased speed of contraction. Too great heat (above 42° C.) induces *heat rigor*, from the coagulation of the muscle proteins.

4. *The effect of two successive stimuli.*—If a second stimulus is applied less than $\frac{1}{200}$ second after the first, there is no response because the muscle is refractory during this period; but if the second follows at a sufficient interval of time, each will cause a twitch and two simple muscle curves will be written (fig. 13, A); the second is a little bigger than the first (beneficial effect of contraction). If the second stimulus arrives before the muscle has finished contracting under the influence of the first, a second curve will be added to the first (fig. 13, B). This is called *superposition*, or *summation of effects* and occurs with both maximal and minimal stimuli.

If the two stimuli are in such close succession that the second occurs during the latent period of the first, the result will differ

* Weaker stimuli are known as subminimal.

according as the stimuli are maximal or submaximal. If they are maximal, the second stimulus is without effect; but if submaximal, the two stimuli are added together, and though producing a simple muscle curve, produce one which is bigger than either would have produced separately. This is called *summation of stimuli* (fig. 13, C).

5. *Effect of more than two stimuli.*—If a succession of stimuli is sent into a muscle, or its nerve, the results obtained depend on the rate at which the stimuli follow one another. If the time-

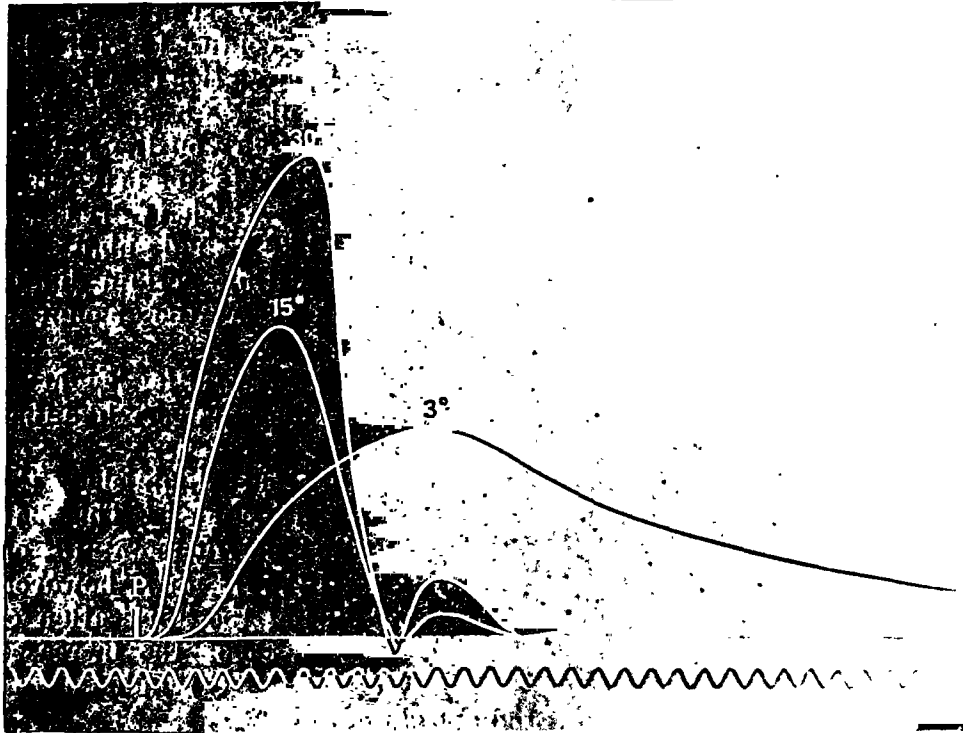


FIG. 12.—Effect of temperature on the simple muscle curve. The various temperatures are marked on the curves. P is the point of stimulation; and the time-tracing scale indicates hundredths of a second. (See Text.)

intervals between the stimuli are sufficiently great, each stimulus will produce a simple muscular contraction. A succession of twitches is recorded and the *beneficial effect of previous action* is exhibited in what is known as a *staircase effect* (fig. 14, A and B).

If the induction shocks follow each other more rapidly, the effect is a continuation of the superposition curve already described in connection with two successive stimuli. Each successive increment is, however, smaller than the preceding, and at last the muscle remains at a maximum contraction, till it begins to relax from fatigue.

A succession of stimuli may be sent into the nerve of a nerve-muscle preparation by means of an interrupter. This method of

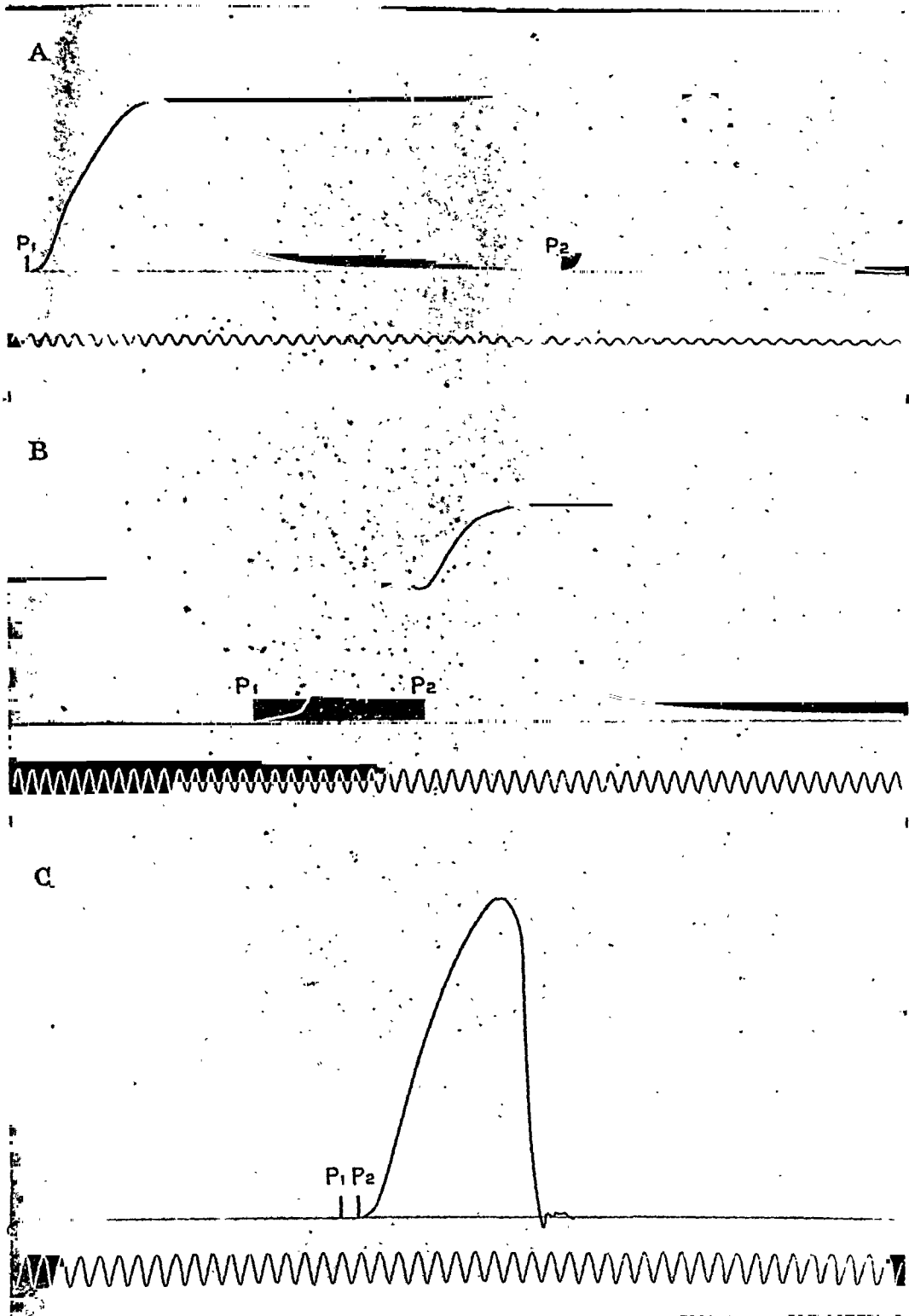


FIG. 18.—Effect of two successive excitations. The two points of excitation (P_1 and P_2) are marked in each case on the base-line. In A, P_1 and P_2 are sufficiently far apart to give separate curves. In B they are nearer together, and superposition is seen. In C they are sufficiently near to give summation of stimuli. Submaximal stimuli were used throughout and the time-tracing in each case shows hundredths of a second.

stimulation is called *faradisation*. When the stimulation is slow the number of contractions corresponds to the number of stimulations (fig. 14); the condition of prolonged contraction so produced, the muscle never relaxing completely between the individual contractions of which it is made up, is called *tetanus*: *incomplete tetanus*, when the individual contractions are discernible (fig. 14, C, D, and E); *complete tetanus*, as in fig. 14, F, when the contractions are so rapid that they are completely fused to form a continuous line without waves.

These results apparently depend on the accumulation and disappearance of acetyl-choline at the nerve-endings. This substance apparently acts as a chemical mediator between the nerve and the muscle.

The rate of stimulation necessary to cause complete tetanus varies considerably; for frog's muscle it averages 15 to 20 per second; for the pale muscles of the rabbit, 20 per second; for the more rapidly acting muscles of the cat, *e.g.* the internal rectus of the eye, over 100 per second may be necessary (Cooper and Eccles). The rate necessary to produce complete tetanus is diminished in a fatigued muscle as its period of relaxation is prolonged.

It will be noticed in class work, and in fig. 14 B, that when the tetanus is incomplete there is a tendency for the muscle to shorten—*i.e.* the relaxation is less rapid. This is in part due to fatigue but it is also due to the onset of the phenomenon of *contracture*. This contracture is an active contraction involving increased metabolism and it is suggested that permanent changes in the membranes of the muscle have occurred. It is readily produced or increased by certain chemicals.

Voluntary Contraction.—There is evidence that voluntary contraction, that is a muscular contraction made by an effort of will, is essentially tetanic in nature. This is best shown by counting the number of electrical variations which accompany a voluntary contraction, on the assumption that each fundamental unit of the contraction has an electrical change as its concomitant. This can be accomplished by the use of a very delicate galvanometer. The number of electrical variations is then found to be a high one. More recently Adrian and Bronk have recorded the current of action of a single muscle-fibre by using a special electrode, which can be plunged into the muscle, and magnifying up the current produced by a valve amplifier. Different muscles appear to vary, but the average number of electrical variations is about 50 per second.*

This view of the tetanic nature of voluntary contraction is supported by the fact that some nerve-cells when stimulated reflexly do not discharge single impulses but groups of impulses.

A voluntary contraction probably differs from experimental tetanus in that in voluntary contraction the fibres of the muscle

* Gasser and Newcomer found that impulses of 70 per second were produced by the diaphragm.

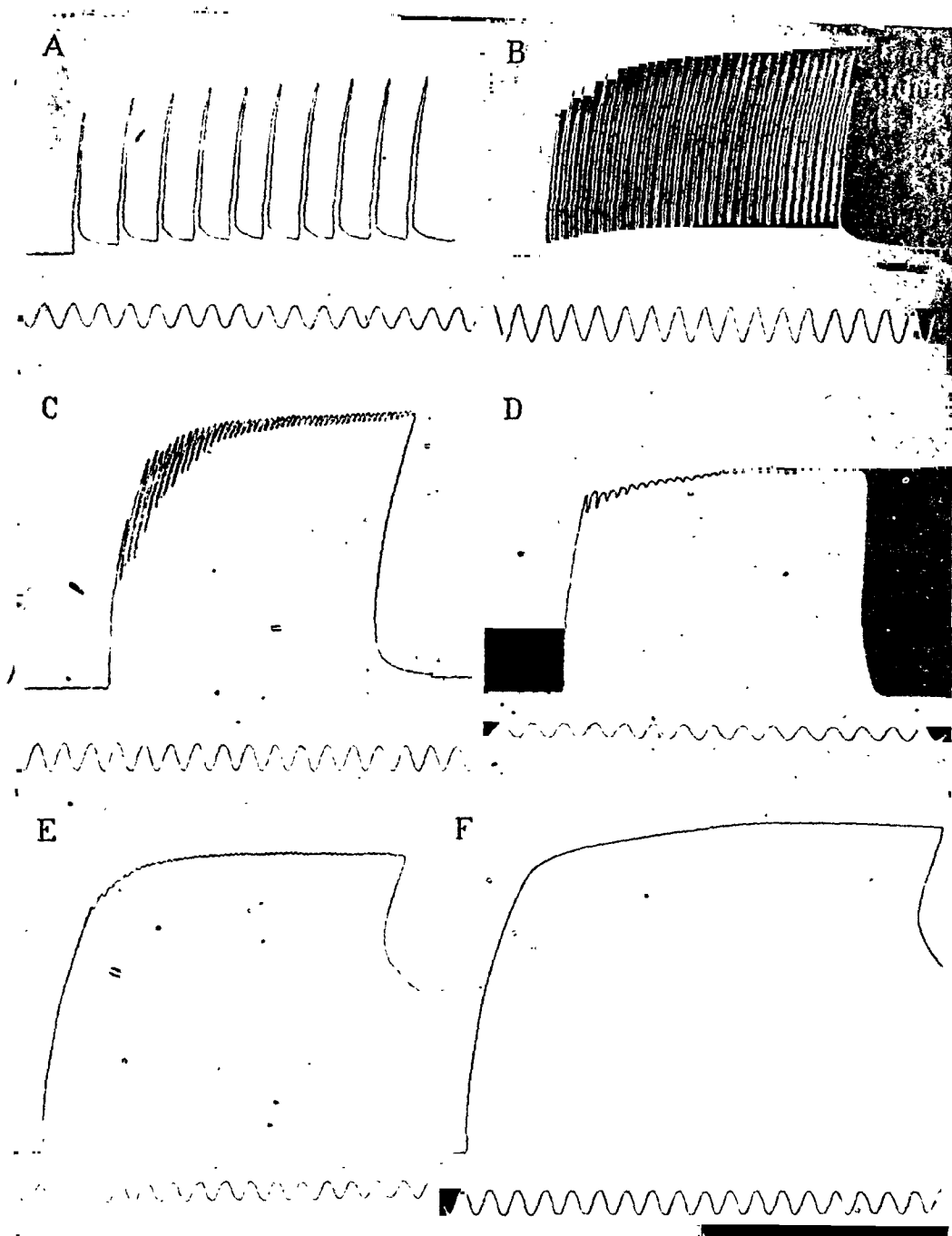


FIG. 14.—Composition of tetanus. These six tracings were obtained on a slowly moving drum from a frog's gastrocnemius, which was excited by a succession of induction shocks. By a mechanical contrivance the rate of the vibrating spring which interrupted the primary circuit of the inductorium could be easily varied; and the rate of the hammer was increased from about 1 per second in A to 30 per second in F. In A, separate twitches are seen; in B, the rate was still insufficient to cause fusion; in both A and B, the staircase effect is well seen. In C and D, the rate was sufficiently great to cause incomplete tetanus; in E, tetanus was nearly complete, and in F it was complete. The time-tracing in each case shows half-seconds.

are stimulated in relays intermittently because all the cells of the spinal cord which control the muscle do not receive this stimulus simultaneously (see motoneurone pool). This is suggested by the fact that a voluntary movement can be maintained for a relatively long period and also by the irregular nature of action currents of a voluntary contraction compared with the regular nature of the responses in experimental tetanus. In the latter fatigue occurs relatively rapidly because the stimulus even when submaximal is always applied to the same fibres which contract fully.

On the other hand, we know that in a voluntary contraction

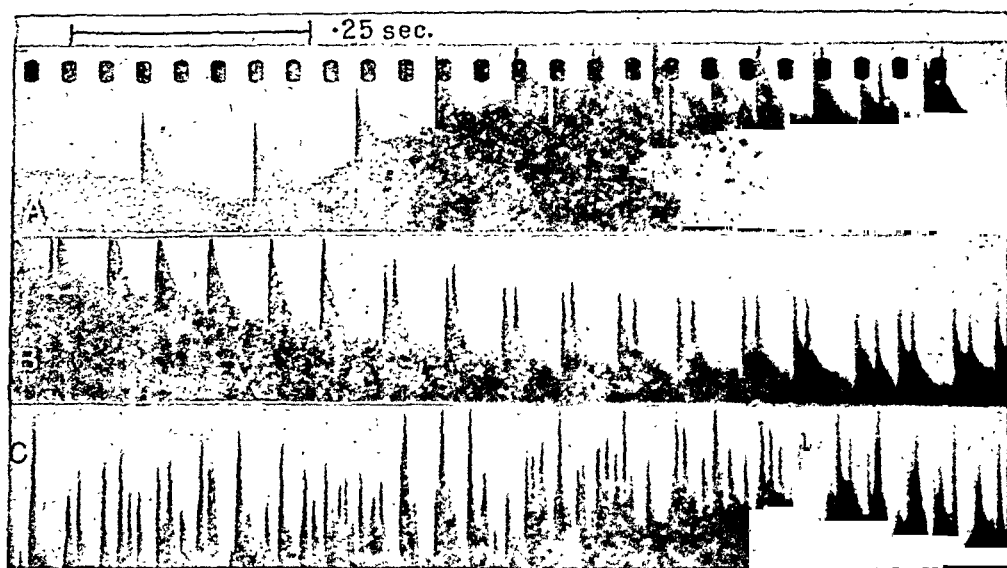


FIG. 15.—Action currents from human triceps (E.D.A.) recorded with concentric needle electrodes during voluntary contraction gradually increasing in power from A to C. (Adrian and Bronk.)

there is not a single nerve unit at work but probably several which play an important part in co-ordinating and grading the degree of contraction with that of other muscles.

Sherrington has found that certain nerve-cells (those concerned with extensor reflexes) have an inherent rate of rhythmic discharge which is unalterable, while others (those concerned with flexor reflexes) have a rate which can be masked completely by imparting to the sensory nerve in a reflex preparation other rates up to quite high figures (100 vibrations per second or more). In fact, in the flexors the rate of the muscular contractions under artificial shocks exactly corresponds to the rate of the stimuli whether they are applied to the motor nerve or to the sensory nerve in the reflex arc. A twitch, however, is never elicited reflexly.

Lever Systems.—The arrangement of the muscles, tendons, and

bones presents examples of the three systems of levers which will be known to anyone who has studied mechanics; the student of anatomy will have no difficulty in finding examples of all three systems in the body. What is most striking is that the majority are levers of the third kind, in which there is a loss of the mechanical advantage of a lever, though a gain in the rapidity and extent of the movement.

Most muscular acts involve the action of several muscles, often of many muscles. The acts of walking and running are examples of very complicated muscular actions in which it is necessary not only that many muscles should take part, but that they should do so in their proper order and in due relation to the action of auxiliary and antagonistic muscles.

Elasticity of Muscle.

The danger of tearing in a muscle or its tendon when the muscle contracts is lessened by the fact that the muscle is elastic and extensible—and it may be shown, by measuring the increase in

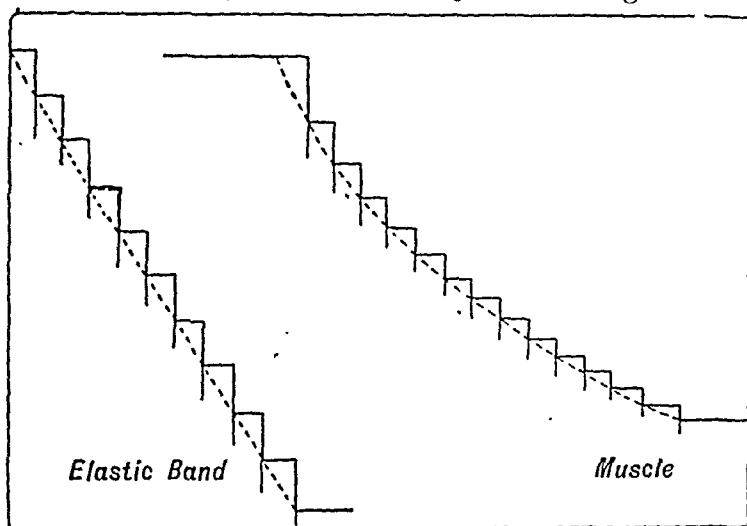


FIG. 16.—(After Waller.)

length which occurs when the muscle is loaded with different weights, that it is more easily stretched relatively when it is contracted than when it is relaxed. Muscle is thus very different from a piece of indiarubber which stretches exactly according to the weight placed on it. Fig. 16 shows the effect of equal increments of weight in indiarubber and in muscle.

The Work and Efficiency of Muscle.

Work done by a muscle may be expressed in foot-pounds or gramme-centimetres according to the height a given weight is

raised, allowance being made for the magnification by the lever. This is the *isotonic method* used in most classes, but it gives only approximate results because of the work done in overcoming the inertia and friction of the lever system.

In more accurate investigations, therefore, the muscle is not allowed to shorten, and the work is measured in terms of the tension exerted at its extremities. This is known as the *isometric method*.

The muscle is made to pull against a spring which it can only move to a very slight extent. The slight movement is greatly magnified by a long lever or by a beam of light reflected from a mirror on the spring.

It is considered better to regard the end-product of muscle contraction as potential energy set free (A. V. Hill). The results are, however, very similar to those obtained by the ordinary isotonic method in which the muscle is allowed to shorten. Many attempts have been made to calculate the energy set free on contraction by making use of the heat produced during contraction. The whole problem is complicated by the fact that in different circumstances different amounts of energy are at the disposal of the muscle and accurate results are therefore difficult to obtain.

The isometric investigations have, however, emphasised that of the total work done by a muscle, only a part appears as external work, *e.g.*, the lifting of a load. A large proportion is required to overcome the viscous resistance of the muscle itself. We may compare the loss to the energy wasted in stirring a viscous fluid compared with a non-viscous fluid at the same speed. Further, the more rapidly we stir, the more energy is wasted in this way. It follows, therefore, that within limits the more slowly a muscle contracts, the more energy appears as external work, and that there is an **optimum rate of contraction**.

It can be shown that human muscles have a similar optimum rate of contraction or speed of movement and that exercise, *e.g.* walking faster or slower than our optimum, is wasteful and involves the use of extra oxygen and fuel. This fact is of great importance in industry, and in long distance racing, although other factors, such as co-ordination of muscles, also enter into the problem. It is interesting to remark that the practical optimum for marching (120 paces per minute) recognised by the Army corresponds to the theoretical optimum found by physiologists. The fatigue we experience from walking very slowly depends on a variety of causes.

A rise of temperature, by increasing the rate of contraction, diminishes the amount of external work done.

In measuring the total realisable work of a muscle accurately, a simple lever system with a fixed load is not satisfactory, since it does not permit of proper utilisation of the elastic energy. This

difficulty is overcome by the use of the inertia lever. By it, the muscle contracts against the inertial resistance of a heavy balanced lever. The muscle has to overcome the inertia of the system at the beginning of the contraction, when its force is maximal, and subsequently has only to accelerate its movement. At each stage of its contraction, the muscle is opposed by a force which it can just overcome. The system may be weighted and the inertia varied, so that the maximum load and the maximum shortening are obtained. Since the inertia and weight of the system are known, the work done can be calculated from the height to which the lever is raised.

In the body some of the muscles act isotonically and some isometrically. For instance, in the muscles which move the arms shortening is important, while in those which move the jaws tension is the more important. The latter are characterised by a large number of short fibres which converge like the barbs of a feather on its quill, while in muscles which shorten greatly the fibres are relatively longer, fewer, and almost parallel. Some muscles are of mixed character.

The effect of load on the work done depends largely on the way in which the load is applied to the muscle. The weight may be allowed to stretch the resting muscle, in which case the muscle is said to be *free-weighted*; or the lever may be supported so that the muscle is not stretched until the contraction begins. Then the muscle is said to be *after-loaded*.

The following figures are taken from an actual experiment done with free-weighted gastrocnemius by the isotonic method (Weber):—

Weight lifted.	Height.	Work done.
5 grammes	27.6 millimetres	138 gramme-millimetres
15 "	25.1 "	376 "
25 "	11.45 "	286 "
30 "	7.3 "	219 "

The work done is found by multiplying the weight by the height through which it is raised. In carrying out the experiment allowance must be made for magnification, which depends on the length of the lever.

The work increases with the weight up to a certain maximum, after which a diminution occurs, more or less rapidly, according as the muscle is fatigued.

If the load is allowed to stretch the resting muscle it is found that the mechanical work performed is increased and it is to be observed that when we wish to obtain the maximum effect we

commonly stretch our own muscles prior to use. It will be seen later that this ability of muscle to respond within certain limits to increased load is of great importance in the case of the heart and the intestine.

By the isometric method it is shown that there is an optimum length at which a maximum tension is produced, and it has been found by Hartree and Hill that at the optimum length the largest amount of heat is produced. An increased load up to a certain point also increases the work done by slowing down the rate of contraction, for as we have seen slow contractions are more economical than fast as less heat is produced in overcoming viscosity.

The muscle, regarded as a machine, is sometimes compared to artificial machines like a steam-engine. A steam-engine is supplied with fuel, the latent energy of which is transformed into work and heat. The carbon of the coal unites with oxygen to form carbonic acid, and it is in this process of combustion or oxidation that heat and work are liberated. Although the analogy between muscle and a steam-engine is by no means an exact one, nevertheless it may stand for our present purpose (see A. V. Hill).

Relaxation.—So far we have been speaking as though the only active phase of muscular contraction were the period of shortening. It is, however, extremely probable that lengthening is also an active process. This was originally mooted by Fick, who pointed out that the fall of a muscle lever during the relaxation period is of variable speed, and is obviously not due to the passive elongation of the muscle by gravity; the way in which this part of the curve is varied by such agencies as temperature, and drugs like veratrine, also indicates that relaxation is an independent process.

The Electrical Phenomena of Muscle.

We have seen that the chemical processes occurring in muscular contraction lead to a transformation of potential energy into work and heat. These changes are accompanied by electrical disturbances also.

The history of animal electricity is really part of the history of the discovery of electricity. It dates from 1786, when Galvani made his first observations. Galvani was Professor of Anatomy and Physiology at the University of Bologna, and his wife was one day preparing some frogs' legs for dinner, when she noticed that the apparently dead legs became convulsed when sparks were emitted from a frictional electrical machine which stood near. Galvani then wished to try the effect of lightning and atmospheric electricity on animal tissues. So he hung up some frogs' legs to the iron trellis-work round the roof of his house by means of copper hooks, and saw that they contracted whenever the wind blew them against the iron. He imagined this to be due to electricity secreted

by the animal tissues, and this new principle was called *Galvanism*. But all his contemporaries did not agree with this idea, and most prominent among his opponents was Volta, Professor of Physics at another Italian university, Pavia. He showed that the muscular contractions were not due to animal electricity, but to artificial electricity produced by contact with different metals.

The controversy was a keen and lengthy one, and was terminated by the death of Galvani in 1798. Before he died, however, he gave to the world the experiment known as "contraction without metals," which we shall study presently, and which conclusively proved the existence of animal electricity. Volta, however, never believed in it. In his hand electricity took a physical turn, and the year after

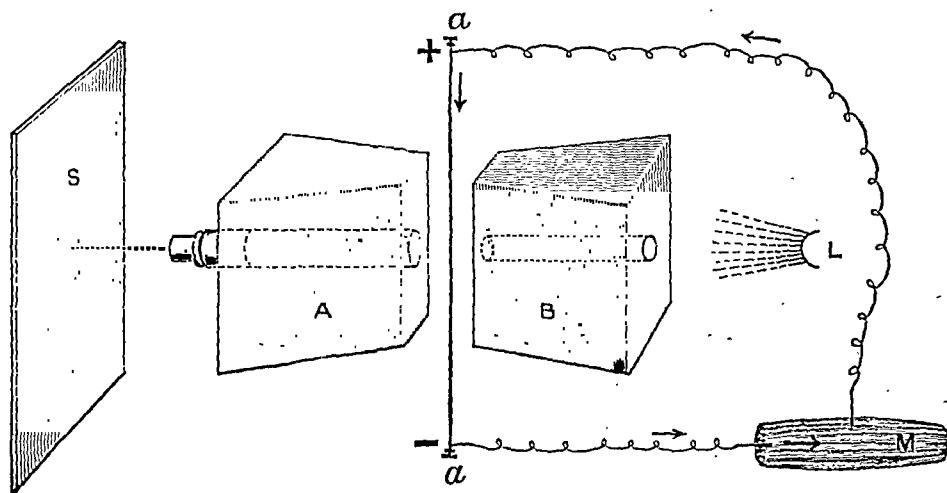


FIG. 17.—Diagram of string galvanometer arranged to show the current of action of an injured muscle. *a, a* is the silvered quartz string; *A* and *B* are the electro-magnets; a microscope is placed in the hole bored through *A*; *L* is a source of light, and *S* the screen upon which the magnified image of the string falls; *M* is the muscle.

Galvani's death he invented the Voltaic pile, the progenitor of our modern batteries. Volta was right in maintaining that galvanism could be produced independently of animals, but wrong in denying that electrical currents could be obtained from animal tissues. Galvani was right in maintaining the existence of animal electricity, but wrong in supposing that the contact of dissimilar metals with tissues proved his point.

This conclusion has been arrived at by certain new methods of investigation. In 1820 Oersted discovered electro-magnetism: when a galvanic current passes along a wire near a magnetic needle, the needle is deflected one way or the other, according to the direction of the current. This led to the invention of the astatic needle and the ordinary mirror galvanometer which is used in every physical laboratory for the detection of small electric currents.

The String Galvanometer.—In the ordinary galvanometer, by

which electric currents may be detected, the current passes through a fixed coil of wire, and deflects a small magnetic needle suspended in the centre. This arrangement can be inverted, the magnet being large and fixed, and the coil small and movable. The string galvanometer of Einthoven is a development of this type. The coil is reduced to a single thread of glass (a , a fig. 17), coated with gold on the surface so as to conduct the current. In less delicate apparatus a copper or platinum string may be used. It hangs between two large electro-magnets which give a very intense "field." Whenever a current passes along the thread, it moves across the magnetic field, the side to which it moves varying according to the direction of the current. The thread is illuminated by a strong light, and magnified by a microscope, which throws the image on to a screen. If a

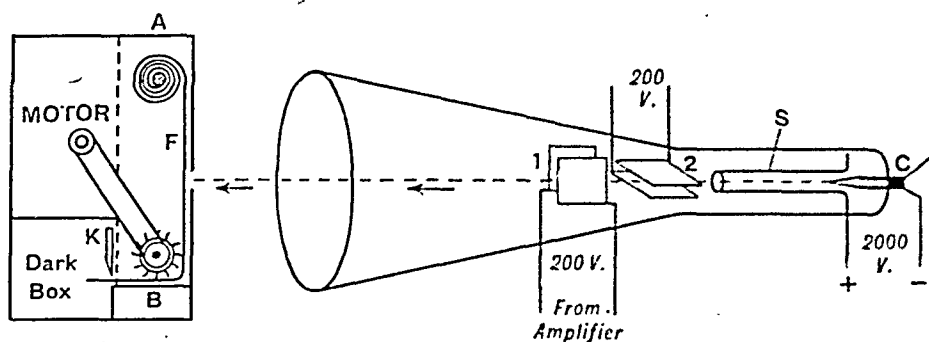


FIG. 18.—Diagram of cathode ray tube. Electrons are emitted from the filament C and pass through the metal shield S to be converted into a beam of light by the fluorescent screen at the end of the tube and projected on the film of the camera F. The beam is deflected vertically for centering by the plates 2, and by the amplified current laterally by the plates 1. The film of camera is driven by a clockwork motor into the dark box and may be cut off in sections as used by the knife K. The dark box, which is in a separate compartment, is removable.

record of the movements is desired, the shadow of the string is thrown upon a slit behind which is a vertically moving photographic plate. The string galvanometer in hospital is extensively used for recording the currents of action of the heart, but is being replaced by the more robust cathode ray oscillograph, which has been greatly developed because of its use in television, radiolocation and the like.

The Cathode Ray Oscillograph will probably replace all other means of electrical recording, since having no moving parts its records are instantaneous and it is much less easily broken than the extremely delicate string of the string galvanometer. A cathode ray apparatus consists essentially of a beam of electrons emitted in a vacuum from a filament. The beam passes between plates and the application of a potential difference to the plates causes the beam to be deflected, the deflection being recorded on a moving photographic film. The currents must first be magnified by a valve amplifier.

Non-Polarisable Electrodes.—If a galvanometer is connected with a muscle by wires which touch the muscle, electrical currents are obtained in the circuit which are set up by the contact of metal with muscle. The currents so obtained form no evidence of electromotive force in the muscle itself. Moreover, the passage of an electric current through the tissue causes electrolysis with the movement of ions, the positive ions (*e.g.* Na') passing to the kathode, the negative (*e.g.* Cl') to the anode. There they give up their charges and chemical reactions occur, so that a minute gas battery is formed which interferes appreciably with the current under investigation. By the use of non-polarisable electrodes this may be prevented. In modern work silver chloride electrodes are used. These consist of silver wire previously coated electrolytically with silver chloride.

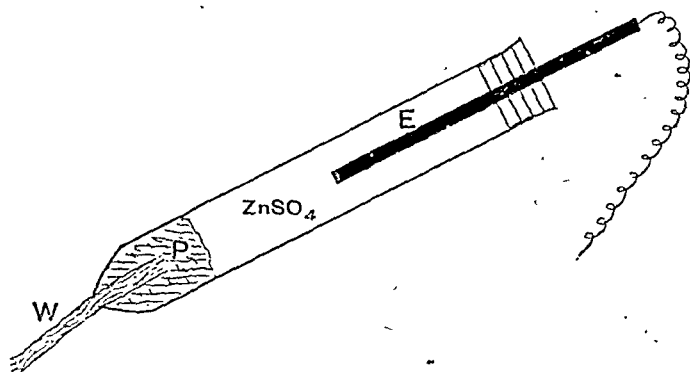


FIG. 19.—One of a pair of non-polarisable electrodes. In this form a zinc rod dips into zinc sulphate in a piece of glass tubing one end of which is closed by a cork and the other with kaolin soaked in saline. Out of the latter there pass to the muscles or nerve a few strands of fat-free wool soaked in saline. Any Zn which is set free becomes deposited in the electrode and any SO_4 in the other electrode acts on the electrode slightly. The production of gas is thereby avoided.

When, therefore, sodium chloride is broken up the Na' and Cl' ions merely form sodium chloride and silver chloride and no further reaction takes place. In the older form of Du Bois Reymond amalgamated zinc dipping into zinc sulphate solution was connected to the tissue by china clay soaked in physiological salt solution. Electrodes on this principle are still used in taking records of heart currents.

Fig. 19 shows a convenient form of the latter variety.

Current of Action.—In a muscle removed from the body it is found that on leading off two parts of its surface to a galvanometer, the needle (or in the string galvanometer, the string) usually moves; this indicates that the two parts of the muscle are not in the same state of electrical potential, and therefore a current flows when the two parts are connected by a conducting wire; the most marked result is obtained when the longitudinal surface is connected with one or other of the cut ends as in fig. 17. This is

the *current of injury*; an injured portion of a muscle, such as the cut end, resembles the zinc in a zinc-copper cell, and is therefore *galvanometrically negative* in contrast to the uninjured centre. The longitudinal uninjured surface thus corresponds to the copper of a Daniell cell, and the electrode attached to it is the positive pole; it may therefore be spoken of as *galvanometrically positive*. This is indicated in the diagram by the + and - signs, and the direction of the current is shown by arrows.*

Du Bois Reymond further demonstrated that when the injured muscle showing its injury current was made to contract tetanically, a current was set up in the opposite direction which caused the galvanometer needle to return towards its previous position. This lessening of the injury current he spoke of as the *negative variation*,

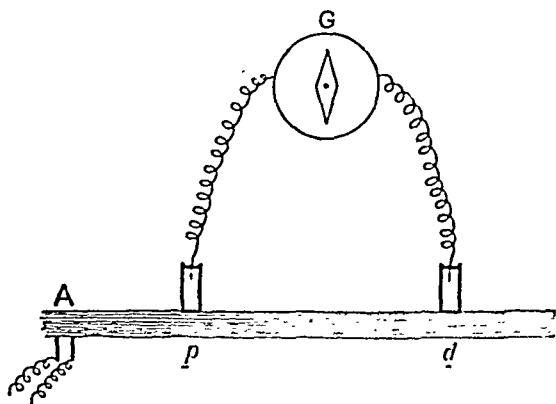


FIG. 20.

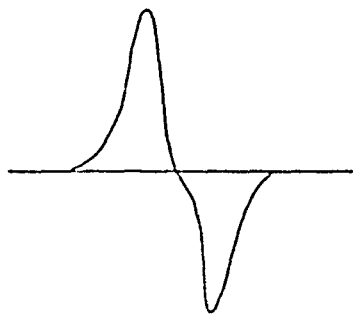


FIG. 21.—Biphasic curve of the normal sartorius. (After Keith Lucas.)

but it is now more usually termed the *current of action*. The essential cause of the current of action is that active portions of a muscle become (like injured portions) galvanometrically negative in contrast with the portions of the muscle which are at rest.

The electrical change during a twitch is called a *diphasic variation*. The contracting part of a muscle becomes first more negative (galvanometrically); it then rapidly returns to its previous condition. The change indicates a disturbance of the stability of the tissue; its disappearance is the result of a return of the muscular tissue to a state of rest. If the muscle is stimulated at one end, a wave of contraction travels along it to the other end. The electrical variation travels at the same rate as the visible contraction, but precedes it.

Suppose two points (*p* and *d*) of the muscle (fig. 20) are

* It will be realised that since it is now known that negative ions "flow" to the positive and not the reverse, the current is really "flowing" through the galvanometer in the proper direction.

connected by non-polarisable electrodes to a string galvanometer, and that the muscle-wave is started by a single stimulus applied at A ; just before the visible wave reaches p this point becomes galvanometrically negative to d , and therefore a current flows from d to p through the galvanometer G . A moment later the two points are equi-potential and no current flows; a minute fraction of a second* later this balance is upset, for when the wave reaches the point d , that point undergoes the same change, and the galvanometer needle moves in the opposite direction.

If, however, instead of examining the electrical change in the muscle in the manner depicted in fig. 20, one electrode is placed on

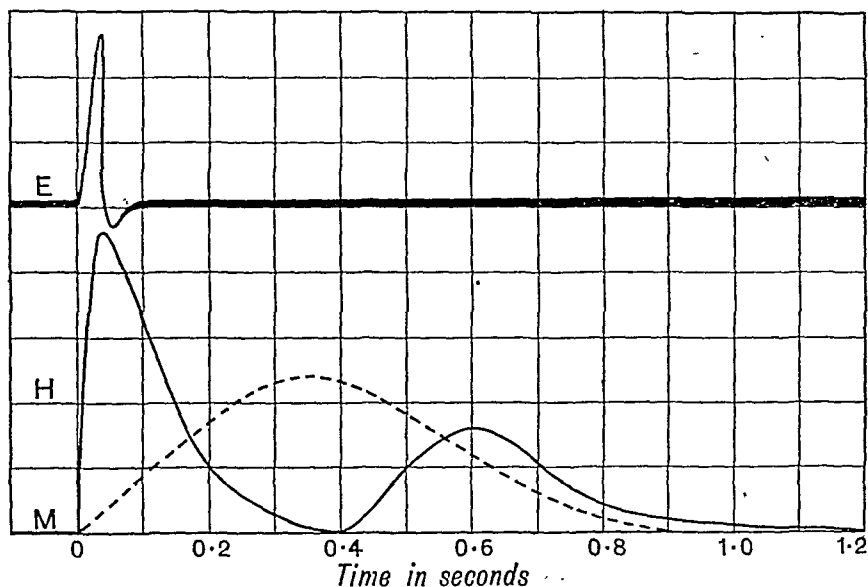


FIG. 22.— M indicates the mechanical response of the muscle, H the rate of heat production, and E the electrical change. Note the early electrical change and the initial and delayed heat. The muscle was stimulated at 0. (After Samojloff, Hill and Hartree.)

the uninjured surface and the other on the cut end, the electrical response is a different one.

Under these conditions, the electrical change is a *monophasic variation*, for when the muscle-wave reaches the cut end, this part of the muscle, owing to its injured state, does not respond to the excitatory condition; and the electrical response is also extinguished. If the muscle is thrown into tetanus a series of monophasic variations is produced.

The employment of instruments of precision, like the string galvanometer or oscillograph has enabled investigators to ascertain the time of onset and duration of the electrical disturbance; this precedes the actual shortening of the muscle, occurring chiefly

* The time varies with the distance between p and d .

during the latent period, and it is completed long before the visible contraction is over. This is well shown in the preceding diagram (fig. 22) in which the muscle curve (M) is seen with its accompanying electrogram taken with the string galvanometer.

Muscle is not the only tissue which exhibits electrical phenomena. A nerve which is uninjured is iso-electric; injury causes a current of injury; activity is accompanied by a similar diphasic wave travelling along the nerve simultaneously with the nervous

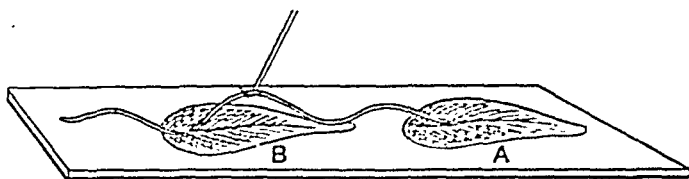


FIG. 23.—Galvani's experiment without metals.

impulse. The activity of secreting glands, vegetable tissues, retina, etc., is accompanied by somewhat similar electrical changes, which we shall study in detail later.

The most prominent exhibition of animal electricity is seen in the electric organs of electric fishes. In some of these fishes the electric organ is modified muscle, in which a series, as it were, of hypertrophied end-plates corresponds to the plates in a voltaic pile. In other fishes the electric organ is composed of modified skin glands.

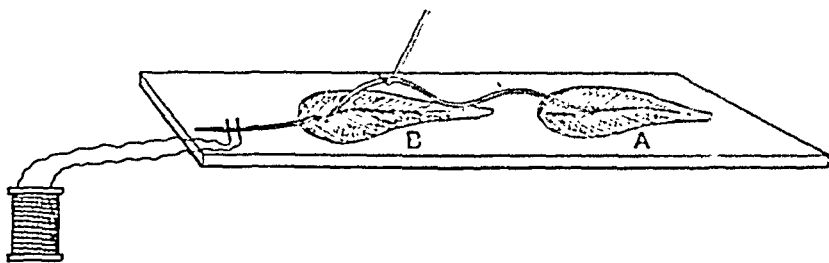


FIG. 24.—Secondary contraction. (After Waller.)

But in each case the electric discharge is the principal phenomenon that accompanies activity.

Galvani's contraction without metals. If the nerve of a nerve-muscle preparation A is held by a glass hook upon another muscle B (fig. 23) or upon its own muscle, it will be stimulated by the injury current of the muscle on which it is held, and this leads to a contraction of the muscle (A) which it supplies. The experiment succeeds best if the nerve is dropped across a longitudinal surface and a freshly made transverse section.

Secondary contraction. This is caused by the current of action. If, while the nerve of A is resting on the muscle B (fig. 24), the latter is made to contract by the stimulation of its nerve, the nerve

of A is stimulated by the electrical variation which accompanies the contraction of the muscle B, and so a contraction of muscle A is produced. This is called *secondary contraction*.

Chemical Changes in Muscle.

In an earlier section it has been stated that the energy of muscle contraction is derived from the burning of carbon and hydrogen to carbon dioxide and water, but it has become evident that many other changes occur and these are of interest because they give a clue to the obscure problem of the nature of muscle contraction.

Apart from the contractile element in muscle it is now known that there occur in resting muscle three substances which are broken down during contraction, adenylyl pyrophosphate, creatine phosphate, and glycogen. The first two are completely restored during recovery, the glycogen only partly so, the remainder of the latter being the essential source of the chemical energy.

The most important early observations on the subject were made by Fletcher and Hopkins, in 1907, who found that a muscle would contract in an atmosphere of nitrogen, in which circumstances lactic acid accumulated and the muscle would not recover in the absence of oxygen. It appeared most likely that this liberation of lactic acid was an essential process in the mechanism of contraction and many theories, especially those of Hill and Meyerhof, were built up on this hypothesis. The experiments showed clearly that the oxidation process was not essential for the contraction but for the recovery.

A complete revolution in our ideas of the subject occurred, however, when it was found, in 1930 by Lundsgaard, that a muscle poisoned with iodoacetic acid would contract in the absence of oxygen although no lactic acid was formed. Attention was then paid to the other changes which occurred in the muscle.

It had been observed, in 1914 by Emden in Germany, that the addition of phosphate to muscle juice containing glycogen caused the latter to be broken down to lactic acid with the liberation of phosphoric acid through an intermediate stage of hexose phosphate which was called lactacidogen. A study of the phosphates of the muscle had led to the discovery, in 1927, by the Eggletons in London, and by Fiske and Subbarow independently in America, of creatine phosphate which was broken down by contraction to creatine and phosphoric acid, and rebuilt during recovery. This was then thought to be most intimately concerned with the contraction, and gained support from the findings that, in a poisoned muscle deprived of oxygen, the energy released by the muscle was proportional to the creatine phosphate broken down, and that a

poisoned muscle will contract until all the creatine phosphate is broken down, when the muscle dies. Later it was found that, like the glycogen, it was not broken down until immediately (20 seconds) after the contraction is over. It will be realised that it is the rapid changes which occur which make the study of this subject so difficult. Much has been done by slowing the processes by cold.

Later Emden discovered adenylyl pyrophosphate which is broken down *during* contraction to adenylic acid and phosphoric acid. The adenylic acid subsequently produces inosinic acid and ammonia.

Thus it is seen that sufficient phosphoric acid is released during or immediately after the contraction for the phosphorylation of the glycogen and its conversion to hexose phosphate.

In the rebuilding process the phosphoric acid is again released to resynthesise the creatine phosphate and adenylyl pyrophosphate. In this two processes appear to be possible. (1) Normally the energy for the rebuilding process would seem to be derived from the oxidation of lactic acid to carbon dioxide and water, but a study of the amounts of glycogen broken down, lactic acid and carbon dioxide produced, indicates that much more lactic acid is produced than is oxidised. In the frog much of the unoxidised lactic acid, possibly as much as four-fifths is resynthesised back to glycogen in the muscle itself, but in the mammal this appears to occur only in the liver and the resynthesis is probably less, for in severe exercise there is a considerable rise of blood lactate and excretion of lactate in the urine. (2) The energy released in the breakdown of the hexose phosphate to lactic acid is considered also to be of value in the resynthesis of the creatine phosphate and adenylyl phosphate, for in a muscle deprived of oxygen or short of creatine phosphate there is a synthesis of creatine phosphate. It is thought that normally about one-third is synthesised in this way.

An attempt to show these changes diagrammatically is given below, the details of the carbohydrate breakdown being omitted for simplicity. They are given in relation to the "Oxidation of Carbohydrates" later.

This view fits in well with the measurements of heat production given in the next section, which indicate that more than half the heat produced by a muscle is evolved during recovery but then only occurs if oxygen is present. There is very little delayed anaerobic heat, the energy being used to drive the synthetic processes in these circumstances.

There is also evidence that the resynthesis of the adenylyl phosphate depends on the reconstitution of the creatine phosphate.

Essentially we do not know whether the changes which take place are the cause or the result of the contraction process, and

still less do we know how the alleged humoral transmitter, acetyl choline, from the nerve to the muscle acts. At the moment of

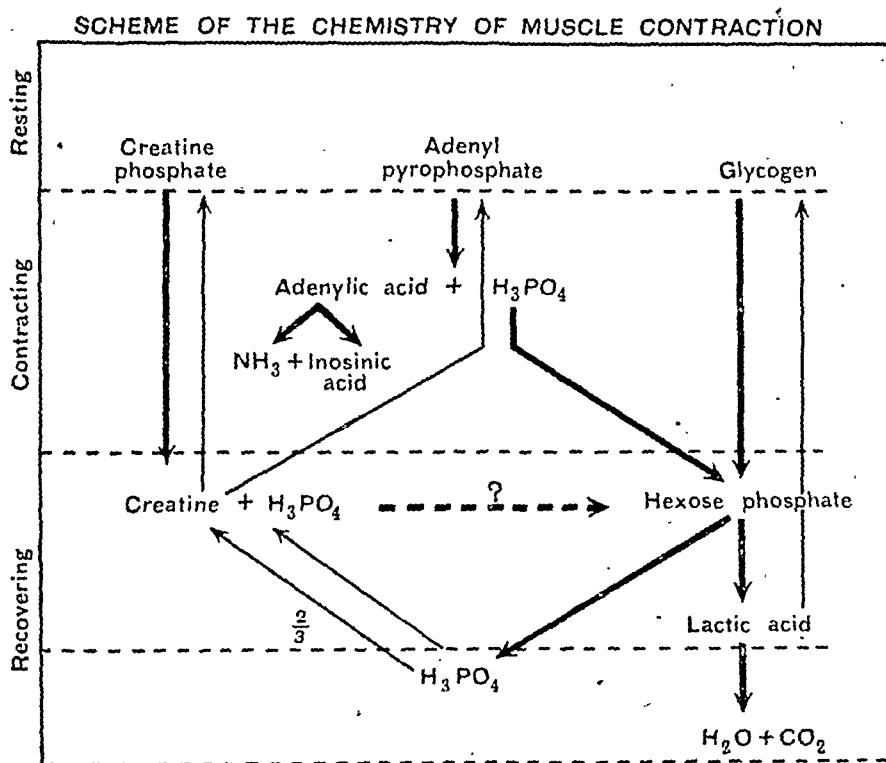


FIG. 25.—The first half of recovery is anaerobic but the second half requires oxygen. The heavy lines indicate breakdown.

writing it would seem that the actual contractile element may be an enzyme, adenyl phosphatase, which suddenly becomes activated.

Oxygen Debt.

From what has been said regarding the oxidation of lactic acid it is seen that the muscle, unlike an internal combustion engine, uses oxygen after the contraction is over to recover and prepare for the next contraction. If oxygen is not sufficient the accumulation of lactic acid represents an oxygen debt, and such a debt can be shown to occur not only in isolated muscle but also in man.

In man, oxygen debts of less than 2.3 litres are not accompanied by the appearance of any lactic acid in the blood. With larger debts the lactic acid accumulation is proportional to the excess of debt over this figure. The "alactacid" debt is probably accounted for by a depletion of the store of creatinephosphoric acid in the muscles (Margaria, Edwards and others).

Normally in severe exercise the circulation carries away neutralised lactic acid which may be resynthesised in other tissues, especially the liver, or may be excreted in the urine.

That carbohydrate is the chief source of muscular energy is shown by the fact that the respiratory quotient $\frac{\text{CO}_2 \text{ given out}}{\text{O}_2 \text{ retained}}$ (see p. 253) during the *total* period of exercise and recovery is unity.

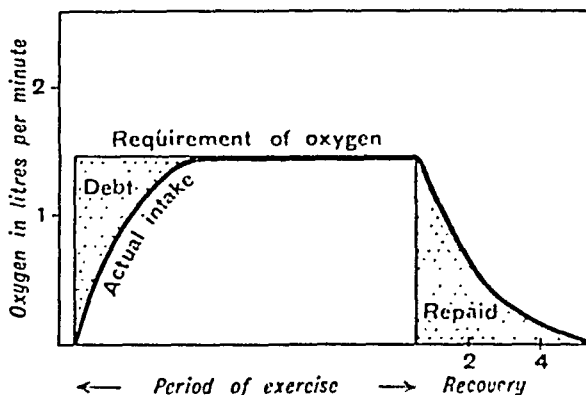


FIG. 26.—Diagram showing oxygen debt (after Hill and Lupton).

If, however, the exercise is prolonged the respiratory quotient may be less than unity, showing that substances other than carbohydrates, notably fat, can be used. During the period of actual exercise the respiratory quotient is often greater than unity; this is especially true of severe exercise, and is to be explained by the increased breathing which causes carbon dioxide to be swept out in unduly large amounts. The increased breathing is due to lactic acid entering the blood and presumably raising its H-ion concentration (Hill, Long and Lupton). Conversely, during the recovery period the R.Q. may fall below unity because of the retention of carbon dioxide in the body. (See Reaction of the Blood.)

Fatigue of Muscle. (See p. 70.)

Thermal Changes in Muscle.

A muscle when uncontracted may not be at absolute rest; chemical changes occur in it, and consequently heat is produced. There is a transformation of the potential energy of chemical affinity into other forms of energy, especially molecular motion and heat. But when muscle contracts, the liberation of energy is increased; work is done, and more heat is produced; the heat produced represents more of the energy than the work done.

On a cold day one keeps oneself warm by exercise; in fact the body temperature may go up temporarily 1° to 2° as a result of muscular activity.

For the detection of small rises in temperature, a *thermopile*, and not a thermometer, is employed.

A thermopile consists of a junction of two different metals such as antimony and bismuth; the metals are connected to a galvanometer. If one junction is heated and the other not an electrical

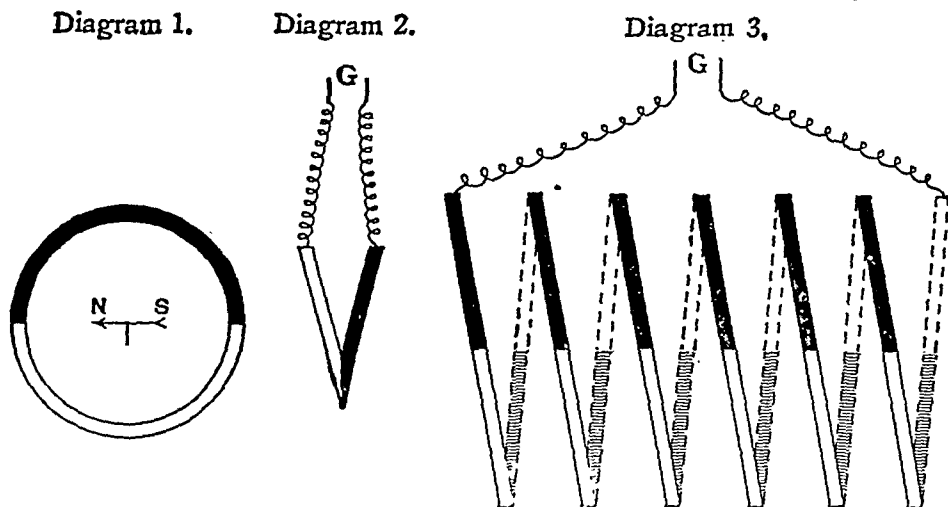


FIG. 27.—Diagrams to illustrate the principle of thermopiles.

current passes round the circuit and is detected by the galvanometer. If the number of junctions in the circuit is increased, and one set is heated, the electrical current is increased through the galvanometer. The arrangement is shown in fig. 27.

Needle-shaped couples may be plunged into the muscles. In modern work the muscles may be laid on a number of junctions in series and wound round a vulcanite support, and the apparatus enclosed in a chamber such as a thermos flask to prevent heat loss (Hill), and keep the outer junctions at constant temperature.

In the thermopile of A. V. Hill,* the combination used is copper or other metal and an alloy known as constantan (an alloy of copper 60 per cent. and nickel 40 per cent.). By employing a large number of such junctions in connection with a mirror galvanometer, it is possible to measure the heat produced even in such small muscles as a frog's sartorius, the amount of deflection by known quantities of heat being subsequently determined. The responses of this delicate instrument are recorded photographically

* A. V. Hill is Foulerton Research Professor of the Royal Society.

and are so immediate that it is also possible to ascertain the exact time when the heat formation occurs.

The important result has been obtained that not only is heat produced during the mechanical response (initial heat), but also after (recovery heat). The latter is associated with the processes which accompany recovery and requires the presence of oxygen; but the initial heat like the contraction is produced independently of the presence of oxygen. The amount of heat is approximately proportional to the duration of the stimulus and to the tension produced. The initial heat depends on (1) contraction, (2) the continuance of contraction in the case of a tetanus, and (3) relaxation. In a tetanus we can say, therefore, that there are four phases of heat production.

The relation of the output of heat to the other changes are seen in fig. 22.

If a muscle is not allowed to shorten when it contracts all the energy expended appears as heat, but if it is allowed to contract at an optimum rate (see p. 30) to prevent loss due to viscosity practically all the initial heat appears as work and it has been calculated that the mechanical efficiency of muscle is on the average about 40 per cent.

An ordinary locomotive wastes about 96 per cent. of its available energy as heat, only 4 per cent. being represented as work. In the best triple-expansion steam-engine the work done rises to 12.5 per cent. of the total energy. Thus muscle is more economical than the best steam-engines. The body has further advantage over any engine, for the heat it produces is not wasted, but is used for keeping up the body temperature, the fall of which below a certain point would lead to death, not only of the muscles but of the body generally.

In most engines much heat is lost and is so much wasted energy. In the body the heat is of value to maintain metabolic processes.

Rigor Mortis.

After death, the muscles gradually lose their irritability and pass into a contracted condition. This affects all the muscles of the body, and usually fixes it in the natural posture of equilibrium or rest. The general stiffening thus produced constitutes *rigor mortis* or *post-mortem rigidity*.

The cause of rigor is the coagulation of the muscle-plasma, which is more fully described in the next section. This coagulation results in the formation of *myosin*, and is gradual in onset. Simultaneously: (a) *the muscles become shortened and opaque*; (b) *heat is evolved*;

(c) *the muscles give off carbonic acid*, and (d) *become acid in reaction* (this is due in part to the formation of sarcolactic acid, and in part to the formation of acid phosphates); (e) *glycogen disappears*.

After a varying interval, the rigor passes off, and the muscles are once more relaxed. This sometimes occurs too quickly to be caused by putrefaction, and there is very little doubt that it is really the first stage in the self-digestion or *autolysis* which occurs in all tissues after death, owing to the presence of intracellular enzymes or ferments. This fact we take advantage of in the "hanging" of meat, especially game which is liable to be tough, to make it tender. It is known that a pepsin-like or proteolytic enzyme is present in muscle, as in many other animal tissues—kidney, spleen, etc. (Hedin)—and that such enzymes act best in an acid medium. The conditions for the solution of the coagulated myosin are therefore present, as the reaction of rigor muscle is acid.

Order of Occurrence.—All the muscles are not affected simultaneously by rigor mortis. It affects the neck and lower jaw first; next, the upper extremities, extending from above downwards; and lastly, reaches the lower limbs; in some rare instances, it affects the lower extremities before, or simultaneously with, the upper extremities. It usually ceases in the order in which it begins: first at the head, then in the upper extremities, and lastly in the lower extremities. It seldom commences earlier than ten minutes, or later than seven hours after death; and its duration is greater in proportion to the lateness of its accession.

The occurrence of rigor mortis is not prevented by the previous existence of paralysis in a part, provided the paralysis has not been attended with very imperfect nutrition of the muscular tissue. In a deeply narcotised, *e.g.* chloralosed, animal the onset of rigor mortis is much delayed, and the tissues may remain excitable for long periods (Hemingway and McDowall). It has been observed by Hoet and Marks that in animals dying after prolonged thyroid feeding or after hypoglycæmic convulsions there is no increased acidity of the muscle, yet rigor occurs; it is suggested that the disappearance of glycogen rather than increased acidity is responsible for the production of rigor mortis, although in ordinary rigor both occur together. Rigor occurs most readily in fatigued muscles, *e.g.* of hunted animals, in which the glycogen content is low and the acidity high. A muscle poisoned with iodo-acetate which prevents the formation of lactic acid remains alkaline when it goes into rigor.

Chemical Composition of Muscle.

The general composition of muscular tissue is :—

Water	75 per cent.
Solids	
Proteins	18 per cent.
Gelatin	} 2 to 5 „
Fat	
Extractives	
Inorganic salts	0·5 „
	} 1 to 2 „
	25 per cent.

The extractives comprise a large number of organic substances, all present in small quantities, some of which are nitrogenous, such as creatine, creatinine, xanthine, and hypoxanthine : the rest are non-nitrogenous—namely, fats, glycogen, glucose, inositol, and the variety of lactic acid known as sarcolactic acid. The inorganic salts are chiefly salts of potassium, especially potassium phosphate.

By fractional heat coagulation and studies of solubilities in neutral salt solutions, Halliburton separated several proteins from muscle plasma—

Paramyosinogen : a globulin which coagulates at 47° C.

Myosinogen : a globulin-like protein which coagulates at 56° C.

Myoglobulin : precipitated by heat at 63° C.

In addition there are albumin and myoalbumin, nucleoprotein from the nuclei, and hæmoglobin from the blood which, with similar pigments, *e.g.* cytochrome, give muscle its red colour. If a muscle be heated in saline while attached to a lever it is seen to go into complete heat rigor in stages corresponding to these coagulations. This shows that proteins of plasma are in the actual muscle substance.

The spontaneous coagulation of muscle known as *rigor mortis*, which occurs at death, is the result of changes in the paramyosinogen and myosinogen. This coagulation of muscle protein corresponds to and is affected by almost the same conditions as the coagulation of the blood, except that myosinogen passes through a soluble stage during which it is coagulated at 40° C.

CHAPTER VI

INVOLUNTARY OR UNSTRIATED MUSCLE

UNSTRIATED muscle is responsible for the movement of a large number of structures especially the tubes of the body. It is composed of long, fusiform cells or fibres (fig. 29), which are not as a rule more than $\frac{1}{800}$ inch long. Each cell has an oval nucleus. The cell substance is longitudinally but not transversely striated, and is covered by a delicate sheath. The fibres are united by cementing material, which is stained by silver nitrate, and is bridged across by fine filaments passing from cell to cell.

Unstriated muscle is sometimes called plain or smooth muscle.

The main difference between voluntary and involuntary muscle is the difference expressed in their names. Voluntary muscle is under the control of that portion of the central nervous system whose activity is accompanied by volition. Involuntary muscle, unstriated and cardiac, on the other hand, may contract independently, but is, as a rule, also under the control of a portion of the central nervous system whose activity is independent of volition.

Another characteristic of involuntary muscle is a tendency to regular alternate periods of rest and activity, or *rhythmicality*.* This is best exemplified in the heart, but it is present in all smooth muscle. In this respect it is like cardiac muscle. Those smooth muscles commonly studied are those of the uterus, the large arteries, the intestine and the retractor penis (of the cat or dog). They are chosen because of the ease with which their movements can be recorded when they are removed from the body. In the body, however, it is possible to devise means of recording or observing the movements of many of the internal organs, but their reactions are usually complicated by their environment.

The usual **method of studying smooth muscle** is to suspend it in a bath of Ringer's solution (*i.e.* a saline solution of certain composition) which is kept at the temperature of the animal from which

* Under special conditions, voluntary muscles may show rhythmicality. If one end of the sartorius of a curarised frog is dipped into *Biedermann's fluid*, it contracts rhythmically in a manner analogous to the heart. This fluid has the following composition:—Sodium chloride 5 grams, alkaline sodium phosphate 2 gr., sodium carbonate 0.5 gr., water 1 litre.

the preparation has been derived and through which oxygen is bubbled. (See Method of Studying Intestinal Movements.)

This method is used extensively in the case of the guinea-pig's uterus upon which drugs like pituitary extract are standardised.

It is indeed possible to obtain nerve muscle preparations of unstriated muscle such as those used by McSwiney, by Robson, and by Finkelmann. These workers used pieces of stomach and of intestine with the vagus and splanchnic nerves attached.

The **properties** of unstriated muscle have been studied particularly by Evans, by Brocklehurst, and by Winton. The *excitability* of unstriated muscle is much less to electrical stimuli than striated muscle. Single induction shocks are often ineffectual in producing contraction while the make of a constant current may act as a stimulus. The break is less effective as it is of shorter duration. The chronaxie of unstriated muscle may be from 1-3 sec. compared with .005 sec. for striated muscle. On the other hand it responds much more readily to chemical stimuli than striated muscle.

Successive effective stimuli are summated very markedly, a completely fused response corresponding to a *tetanus* being obtained by very slow stimuli—about 1 in 10 secs. The duration of the ordinary isotonic response is often very long, but varies very much in different tissues and animals.

Unstriated muscle in the body exhibits the remarkable property of going in a tetanic-like sustained contraction known as *tonus*. A severe variety of this may occur in the case of the large colon when it becomes very irritated and may cause very great pain. In some persons whose abdomens are thin and lax the contracted colon may be felt like a sausage under the hand. After the foetus is born such contraction of the uterus is a most important asset in arresting hæmorrhage. It occurs also in blood-vessels.

The fibres of unstriated muscle are not isolated from each other like those of striated muscle but are linked together into masses or sheets. A *graded response* to different strengths of stimulus is therefore not obtained and there is a tendency for the contraction to spread throughout the whole muscle. Why it is sometimes limited to one region, as in the instance just quoted, is unknown.

Unstriated muscle is markedly affected by compression or *stretching* which acts as a mechanical stimulus. The tension which the muscle develops when it contracts is, as in the case of striated muscle, greatly increased by an increase in its initial length. The powerful contractions of the intestines which are caused by saline purgatives are produced by the stretching which is the result of the saline attracting water into the lumen of the gut. Vegetables and fruit, the cellulose

of which is not digested, benefit intestinal movements in the same way. The uterus may be caused to contract by compressional massage, a procedure commonly adopted.

Within physiological limits unstriated muscle is generally relaxed by *heat*, a fact which is made use of clinically in the relief of spasm. Cold tends to cause contraction, as do also rapid changes of temperature.

Although smooth muscle contracts independently when isolated from the nervous system its contractions tend to be irregular and spasmodic. In the body the smooth muscle of organs is controlled by nerves belonging to the autonomic nervous system. In this way their activities are correlated to the general requirements of the body. There is invariably a dual nerve supply, one of which is inhibitory and the other augmentary. The exact action of these nerves has by no means yet been worked out and is greatly complicated by the fact that not only may the same nerve have different actions on different organs or parts of organs but the action may depend very materially on the state of the organ at the time of experiment, as shown by McSwiney and his co-workers.

Illustrations of the activity of the smooth muscle of the alimentary canal are shown in relation to the movements of the alimentary canal in a later section.

The *thermal and chemical changes* which occur in unstriated muscle are, so far as has been ascertained, essentially the same as those of striated muscle. A particularly interesting fact is, however, that the sustained contraction known as *tonus* apparently takes place with no increased expenditure of energy, nor is there apparently fatigue.

A similar sustained and very economical form of contraction is seen in the mechanism which keeps the shell of an ordinary mussel shut, and also in the rigidity which occurs in the extensor muscles of the limbs of animals when the higher parts of the brain are removed. In the latter case a small amount of extra energy is used (Roaf, Dusser de Barenne), but in the case of smooth muscle or of the mussel no additional energy as estimated by its oxygen consumption is used.

The phenomena of *rigor mortis* in involuntary muscle have not been so fully studied as in voluntary muscle. It has, however, been shown that the chemical composition of involuntary muscle differs in no noteworthy manner from that of voluntary muscle, and on death the muscle becomes acid; such products as carbonic acid and sarcolactic acid are formed. In the stomach, uterus, and rectum, *post-mortem* rigidity has been noted, and it probably occurs in all varieties of unstriped muscle, but commonly this may be due to the fall of temperature.

CARDIAC MUSCLE.

The muscle-fibres of the heart, unlike those of other involuntary muscles, are striated; but although in this respect they resemble the skeletal muscles, they have several characteristics of their own. The fibres, which lie side by side, are united at frequent intervals by short branches (fig. 28), a fact which has a considerable bearing on their function as it ensures that large masses of muscle, in most cases the whole heart, contract at once. The fibres are smaller than those of the ordinary striated muscles, and their transverse striation is less clear. No sarcolemma can be discerned. Each fibre has only one nucleus which is situated in the middle of its substance. At the junctions of the fibres there is a certain amount of cementing material, stainable by silver nitrate. This is bridged across

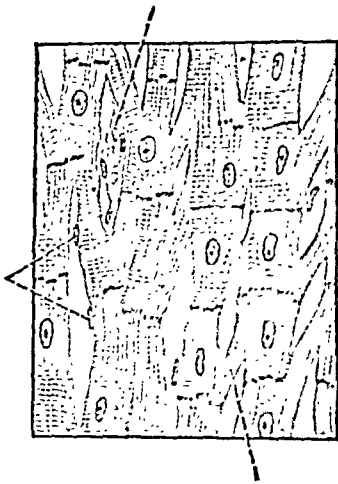


FIG. 28.—Section of heart muscle.

by fine fibrils from cell to cell.

The structure of cardiac muscle gives it very important physiological properties which are more properly studied later in relation to the heart.

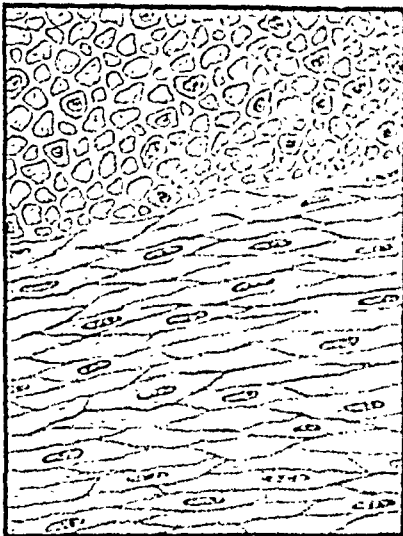


FIG. 29.—Drawing of a section of smooth muscle. Above the section is transverse, below longitudinal.

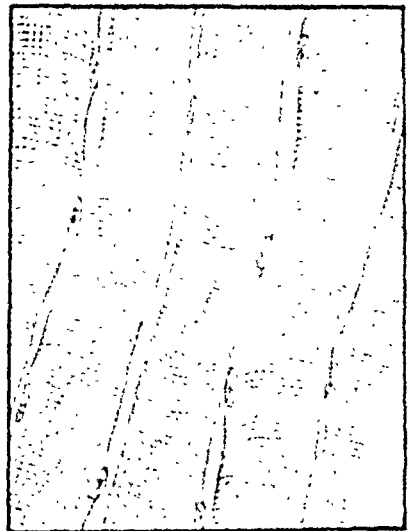


FIG. 30.—Drawing of a section of striped muscle fibres.

DIFFERENCES BETWEEN THE THREE TYPES OF MUSCLE.

The differences between the three types of muscle are indicated in figs. 29 and 30 and in the following table:—

Varieties of Muscle.

Voluntary.	Involuntary.	Cardiac.
Cross-striped separate fibres. Under voluntary control. Not normally rhythmically contractile. Controlled by the pyramidal system of nerves. Not much affected by drugs. Contraction of individual fibres (all or none).	No cross striations, also called smooth muscle. Not under voluntary control. Slow rhythmical contractions. Controlled by the autonomic system. Easily affected by drugs. Contraction of groups of fibres	Cross-striped fibres connected together. Not under voluntary control. Rapid rhythmical contraction. Controlled by the autonomic system. Easily affected by drugs. Contraction of whole heart (all or none) in the lower animals, <i>e.g.</i> frog.

CHAPTER VII

THE NERVOUS SYSTEM

The Structure and Function of a Nervous System

HOWEVER simple, or however complicated, the nervous system throughout the animal kingdom exists for the purpose of co-ordinating and adapting the activities of the animal to its environment, and for the internal regulation of the mechanisms of its body.

A **nervous system**, therefore, consists essentially of afferent nerves which collect impulses from the outside world or from internal organs and transmit them to centres where they are co-ordinated, of intermediate or connecting fibres, and of efferent nerves which distribute impulses to the different parts of the body.

The degree of development of the nervous system in different animals varies enormously according to their needs. It is relatively simple in the lower animals which are not endowed with much power of complicated movement, while it is very elaborate in the higher animals in which there is adaptation to a vast variety of circumstances and activity.

In each instance, however, the basal anatomical unit is the same, namely, the **neurone**, that is the nerve-cell and its processes or nerve-fibres, bundles of which form what we call nerves which we dissect. By some of its processes the nerve-cell receives and by others sends out messages. The processes of one cell form a **synapse** (literally *clasp*) or come into close contact with the processes of other cells, so that messages or nervous impulses may pass from one neurone to another as shown in the following diagram. This division of the nervous system into neurones was originally based on histological evidence. No sign of an actual connection between nerve cells could be demonstrated, but its occurrence was not entirely disproved until it was shown that nerve fibres cut off from their parent cells only degenerated as far as the nearest synapse. It has now been shown that this region of the synapse has a very important physiological function which is discussed later.

In order to permit an efficient interchange of impulses, certain nerve-cells and fibres have been collected together into large masses which constitute the **central nervous system**. This system has been compared, very aptly, with the central telephone exchange of

a town through which one part may be connected with any other. This comparison is, however, very rough as it does not take into account consciousness, which depends on the activity of the brain.

In vertebrates, the central nervous system consists of the brain and spinal cord.

Suppose one wishes to move the arm: the efferent impulse starts in the nerve-cells of the brain, but there are no fibres that go straight from the brain to the muscles of the arm. The impulse travels down the spinal cord, by what are called pyramidal fibres, which form synapses with the nerve-cells of the spinal cord; from these cells fresh nerve-fibres carry the impulse to the arm-muscles. The path is shown in the accompanying diagram (fig. 31). The cell of the motor cortex of the brain is represented by C.C., and its fibre (axon) by P.F. This passes into the white matter of the brain, and travels down the brain stem and spinal cord until it reaches the part of the cord which controls the arm movements, where it terminates by arborising round small internuncial cells (P.C.C.) which form a second relay; thence the impulse is transferred to the large motor-cells (A.C.C.) whose nerve-fibres pass out to the muscles where they end in specialised end plates and where, it is believed, a chemical substance is produced which acts on the muscle fibres. There is as it were a system of relays by which the impulses are distributed to different parts of the body.

One cell may, by means of its processes, be connected with several other cells. For example, the cells in the spinal cord receive messages not only from the brain but

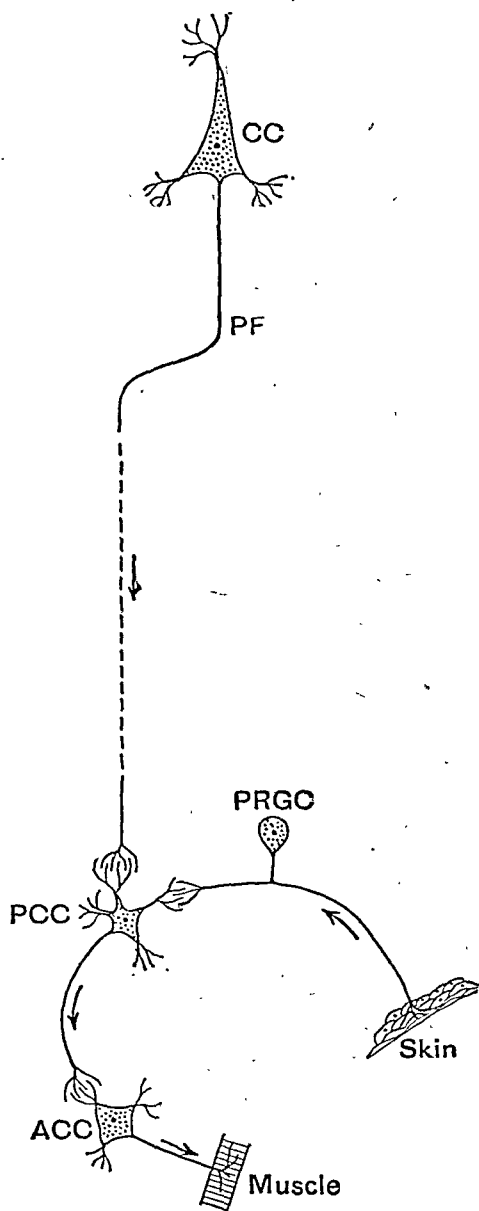


FIG. 31.—Diagram of the neurone of the motor path. For simplification the axon from PRGC is shown to synapse with the same internuncial cell PCC as the fibre of the pyramidal tract. This probably does not actually occur. ACC is a cell representing one of a large motoneurone pool in the region of the anterior horn.

also from other parts of the body (fig. 31). If the finger is pricked an impulse is set up in an afferent nerve or process of a sensory cell and is transmitted to the spinal cord, whence it is relayed to the muscles which cause the arm to be withdrawn. This is known as a reflex act since it does not involve any conscious effort but occurs quite automatically.

The nervous structures involved in such an act we call a **reflex arc**, and consist of a receiving organ and afferent nerve with its cell, an intermediate or connecting nerve and its cell, and an efferent cell and its fibre by which the impulse is sent out to the organ activated.

We shall see that many of the activities of the body are brought about in this way and that the reflex may be looked upon as the **physiological unit** of the nervous system. We shall return to this subject later in considering the Central Nervous System, but meantime these facts must be kept in mind, since many of the processes of the body, *e.g.* the circulation of the blood, are largely controlled by such reflex mechanisms.

For the detailed structure of nerve cells and fibres the student is referred to text-books of Histology.

CHAPTER VIII

PHYSIOLOGY OF NERVE

The nerves which we dissect and study are bundles of processes from nerve cells. Each cell gives off a long process or axis cylinder which is the essential conducting medium, but some nerves, the medullated nerves, have a surrounding myelin sheath which stains with osmic acid, and outside this another thinner sheath, the neurolemma. Non-medullated nerves have no medullary sheath. On section a nerve is somewhat reminiscent of a compound electric cable the fibres of which are insulated from each other and which are bound together into bundles.

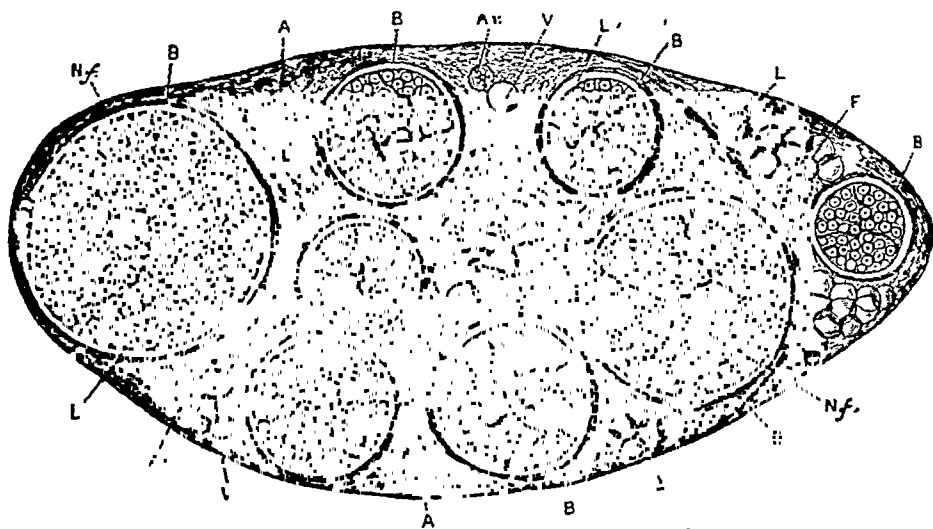


FIG. 32.—Transverse section of the sciatic nerve of a cat, about $\times 100$. It consists of bundles (*funiculi*) of nerve-fibres ensheathed in a fibrous sheath, *epineurium*, A; each bundle has a special sheath (not sufficiently marked out from the *epineurium* in the figure) or *perineurium* B; the nerve-fibres N.f. are separated from one another by *endoneurium*; L, lymph spaces; Ar, artery; V, vein; F, fat. Somewhat diagrammatic. (V. D. Harris.)

Nerve fibres vary very much in size, a fact which is related to their function, as the larger fibres, of the order of $15\text{--}19\ \mu$ which are found in the spinal nerves supplying the voluntary muscles, conduct impulses most rapidly. Smaller fibres, which may be $1.8\ \mu$ to $3.6\ \mu$, exist in the autonomic part of the nervous system. They carry messages to the viscera or internal organs and for the most part are of the non-medullated variety.

Investigation of the Functions of a Nerve

There are two main methods by which the functions of a nerve may be ascertained: (1) *section*, and (2) *stimulation*.

Section.—If a nerve is cut the loss of function that ensues may be observed. Thus, if a motor nerve is cut, motion of the muscles it supplies can no longer be produced by activity of the nerve-centre; the muscle is paralysed. If a sensory nerve is cut, the result is loss of sensation in the part from which it comes.

Stimulation.—In a cut motor nerve, stimulation of the central end (*i.e.* the end still connected with the central nervous system) produces no result; stimulation of the peripheral end produces a nervous impulse which excites the muscles to contract. In a cut sensory nerve, stimulation of the peripheral end has no result, but stimulation of the central end causes a sensation, usually a painful one, and also reflex actions.

Degeneration of Nerve.

When a nerve is cut, there are other results than the loss of function just mentioned; for, even though the nerve is still left within the body with a normal supply of blood, it becomes less and less irritable, till at last it ceases altogether to respond to stimuli.

The part left connected to the parent cell, usually in the central nervous system, remains almost normal; but the peripheral end undergoes what is called, after the discoverer of the process, *Wallerian degeneration*. In the medullated fibres the axis-cylinders fragment and the medullary sheaths break up into droplets of myelin. These changes appear between the first and third days after the section D, the small fibres in general showing the earliest changes; they may readily be detected by staining the myelin droplets black with osmium tetroxide (fig. 33). Initially the changes occur autolytically but later, the droplets are digested and further broken up by the Schwann cells and, in the larger nerves, by invading macrophages. Most of the debris is removed within a month. At the same time, particularly between the fifth and ninth days of degeneration, there is a multiplication of the Schwann cell nuclei. In the non-medullated fibres the fragmented axons are digested by the Schwann cells alone. The endoneurial tubes, which in the normal nerve surround each fibre, remain patent during degeneration, though they shrink in diameter. There is a steady increase in the amount of endoneurial collagen from about the

beginning of the second week of degeneration onwards. Except for precocity in the immediate neighbourhood of the wound, the

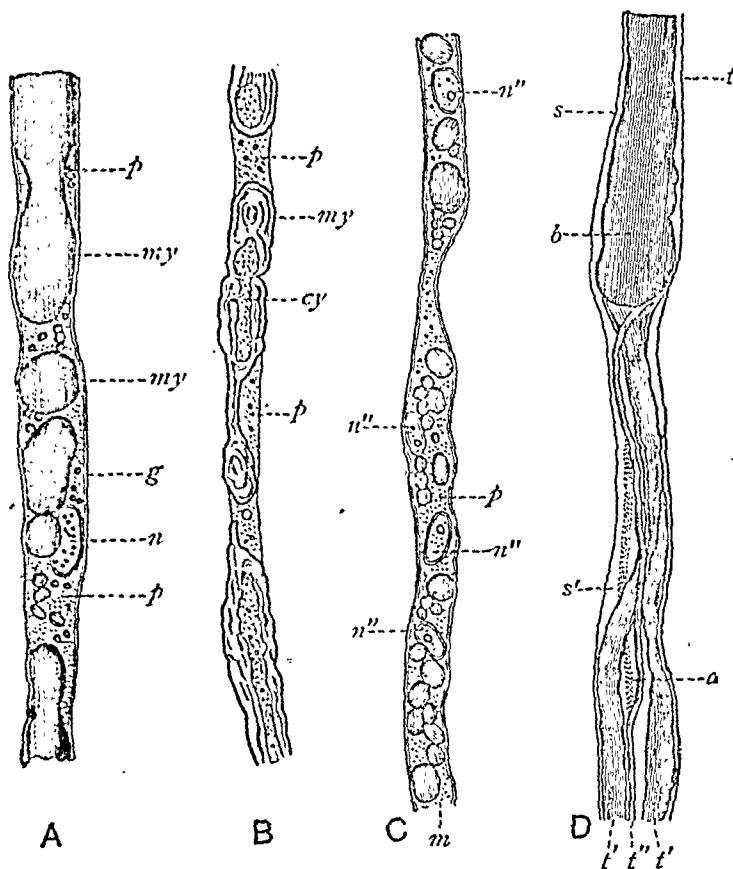


FIG. 23.- Degeneration and regeneration of nerve-fibres. A, Nerve-fibre, fifty hours after operation; my, medullary sheath breaking up into myelin drops; p, granular protoplasm; n, nucleus; g, primitive sheath or neurolemma. B, Nerve-fibre after four days; cy, axis cylinder partly broken up and enclosed in portions of myelin. C, A more advanced stage in which the medullary sheath has almost disappeared; numerous nuclei, n'' , are seen. D, Commencing regeneration; several fibres (t' , t'') have sprouted from the somewhat bulbous cut end (b) of the nerve-fibre; a , an axis cylinder which has not yet acquired its medullary sheath; s , s' , primitive sheath of the original fibre. (Ranvier.)

degeneration occurs simultaneously throughout the whole extent of the peripheral stump of the nerve.

Chemistry of Nervous Tissues.

Nervous tissues contain 65 per cent. to 85 per cent. of water. The first careful study of this subject we owe to Halliburton who showed that grey matter contained a smaller proportion of solid (16·5 per cent.) than white matter (30 per cent.). He showed that in the cerebral grey matter the percentage of protein in the solids was highest (51 per cent.) and consisted mainly of nucleo-protein.

Fat-like substances are also more abundant in non-medullated nerve than in medullated. In the former, as percentages of total solids, there occur cholesterol 47 per cent., lecithin 9·8 per cent., kephalin 23·7 per cent. and galactosides 6 per cent. Various salts and extractives are also present.

When a nerve degenerates the solids become less, in particular the phosphorus content decreases greatly in three weeks.

Regeneration of Nerve-Fibres.

The histological appearance of a degenerated nerve indicates that there is a breakdown not only in an anatomical sense, but in a chemical sense also. As degeneration proceeds, frozen sections made after formol fixation gradually lose the birefringence which is characteristic of normal myelin. The first changes can be detected six to twelve hours after the nerve has been cut, and provide a very delicate test of early degeneration. Staining reactions also change, though these are not consistently visible until at least two days after the nerve has been cut. The reactions most commonly employed are those originating from the technique of Marchi. Intact medullary sheaths blacken in osmium tetroxide (in virtue of the contained phosphatides) but not if the nerve is treated with an oxidising agent (potassium bichromate in Marchi's method), which is usually mixed with the osmium tetroxide. Degenerate medullary sheaths on the contrary blacken even in the presence of an oxidising agent. In the later stages of degeneration the Marchi reaction is not obtained, because the broken-down globules have by that time been absorbed.

After a nerve has been divided, function may be restored by axis-cylinders sprouting from the central stump of the cut nerve, entering and growing down the degenerate peripheral stump, and re-establishing connection with the receptors and effectors. There was formerly much controversy about the origin of the new axis-cylinders, many workers holding that they were formed *in situ* in the peripheral portion. Modern silver methods of staining the young axis-cylinders, however, show clearly that they come from the central stump, and this is supported by observation on living material, which is possible in tadpoles (Williams, Speidel).

All recent work has indeed confirmed the older work in this respect, notably that of Halliburton, who showed that the regeneration of nerve could be prevented by putting a gutta-percha cap on the central stump. He and Mott also showed that if after regeneration the nerve be cut again more peripherally degeneration occurs only on the peripheral side of the second cut.

The work especially of J. Z. Young and of Abercrombie indicates that the following changes occur.

The outgrowth from the central stump, which occurs mainly from the beginning of the second week after the lesion onwards, takes place by an outflow of the material of the axis-cylinders, so that the latter shrink in diameter (Gutmann and Sanders). Each

axis-cylinder as it flows out splits up into a large number (up to 50) of fine fibrils. Meantime the neurolemma cells of the peripheral end have been very active.

Ramifying chains of Schwann cells grow out from the cut surface of the peripheral stump, and are responsible for bridging most of the gap between the two stumps; but they can only reach the sprouting axis-cylinder fibrils and Schwann cells of the central stump (which by themselves do not grow far) if the gap is not too large. Once the regenerating axis-cylinder fibrils meet these chains of Schwann cells they grow rapidly and with little deviation along their surfaces, and are hence directed into the peripheral stump. In the peripheral stump the regenerating fibrils extend rapidly (the fastest at the rate of about $3\frac{1}{2}$ mm. a day) down the persistent neurolemma tubes, which are more or less filled with proliferated Schwann cells. The regenerating fibrils are thus led to the places previously innervated by the nerve. Each neurolemma tube receives several of the regenerating fibrils; there may be 25 in the larger tubes.

Functional recovery depends on the re-establishment of correct peripheral connections for an adequate number of fibrils. The fibres must further return to approximately their correct diameters, on which depend their conduction velocities. In crossing the gap between central and peripheral stumps the regenerating fibrils inevitably become muddled up, and whether they both find tubes which permit them to expand to their right diameter and reach appropriate end-organs depends apparently on chance. The large number of fibrils into which an original axis-cylinder splits as it regenerates greatly increases the probability that each axis-cylinder will eventually establish at least one connection with an appropriate end-organ via an appropriate tube. The large number of new fibrils in each tube are later gradually reduced to few or one. Those which fail to make any peripheral connection apparently disappear; and some of those which make inappropriate connections may also be eliminated. But many inappropriate connections, as well as multiple connections of a single axis-cylinder (resulting from the branching during regeneration) persist. And since in these circumstances relearning seems to be impossible, perfect functional recovery after a nerve has been completely divided probably never occurs. If a nerve has only been crushed, in such a way that the neurolemma tubes remain intact, muddling of the axis-cylinders cannot occur in the injured region; and recovery of function may be complete.

The intrinsic fibres of the central nervous system which have no neurolemma seem to have only a small capacity for sprouting after injury; in the adult brain perhaps none at all (Le Gros Clark). Further, the absence of Schwann cells and of neurolemma tubes

means that even should sprouting occur (as for instance in the regeneration of a dorsal root) there are no pathways to encourage and direct the growing axis-cylinders.

Regeneration leads to a complete recovery of function on the average in from three to twelve months, depending on the length of the nerve and provided the muscles have been prevented from degenerating by electrical stimulation and massage. It grows at about the rate of 1 mm. per day. Sensation returns by stages, crude sensation returning earlier than finer detailed sensation, but the exact cause of this is still under discussion (see General Sensation). Reviews on the subject have been made (Rossi and Gestaldi, 1943, and Young, 1942).

Nerve Crossing.

It has been found possible to attach the centre end of one nerve to the peripheral end of another and to secure complete regeneration of the peripheral end and its function. This was well shown by the experiments of Kennedy and of Langley. The former cut in a dog's thigh the nerves supplying the flexor and the extensor muscles, and sutured them together crosswise. Regeneration of structure and restoration of function occurred as quickly as when the central ends were united to the peripheral ends of their own proper nerves. On examining the cortex of the brain in those animals in which nerve-crossing had been accomplished, it was found that stimulation of the region which in a normal animal gave flexion, now gave extension of the limb, and *vice versa*.

A series of equally important experiments was carried out by Langley, in which he showed that the nerves that supply involuntary muscle behave in the same way. These nerve-fibres will, under certain experimental conditions, terminate by arborising round other nerve-cells than those with which they normally form connections (synapses). It will be sufficient to give one typical experiment. If the vagus nerve is cut across in the neck, its peripheral end degenerates downwards; if the cervical sympathetic is cut across below the superior cervical ganglion, its peripheral end degenerates upwards, as far as the ganglion. If subsequently the central end of the cut vagus is united to the peripheral end of the cut sympathetic, in the course of some weeks the vagus fibres grow into the sympathetic and form synapses round the cells of the superior cervical ganglion, and stimulation of the united nerve now produces such effects as are usually obtained when the cervical sympathetic is irritated; for instance, dilatation of the pupil, raising of the upper eyelid, and constriction of blood-vessels of the head and neck (fig. 34).

Such experiments as these are important because they show that

though the action of nerves may be so different in different instances (some being motor, some inhibitory, some secretory, some sensory, etc.), what occurs in the nerve trunk itself is always the same; the difference of action is due to difference either in the origin or distribution of the nerve-fibres. The familiar illustration in which nerve trunks are compared to telegraph wires, is a helpful one. The destination of a certain group of telegraph wires may be altered, and the alteration may produce different consequences at different places; the electric change in the wires would, however, be the

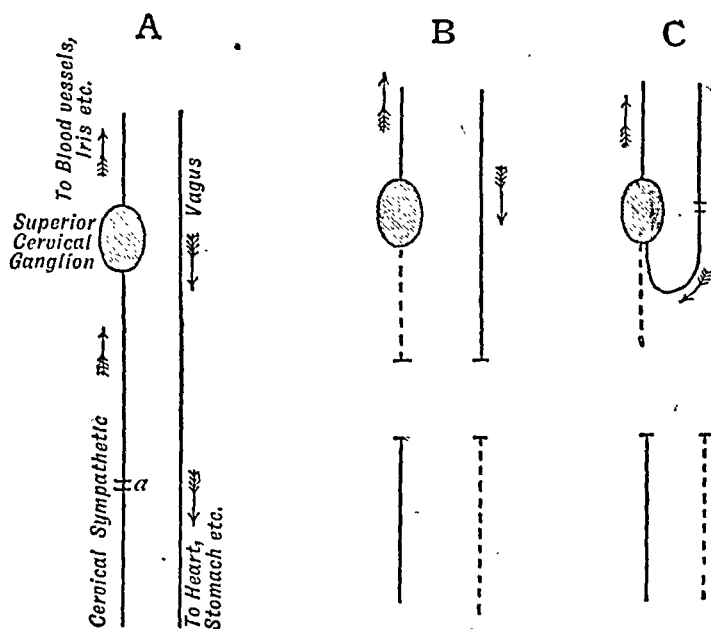


FIG. 34.—Diagram to illustrate Langley's experiment on vagus and cervical sympathetic nerves. In A, the two nerves are shown intact; the direction of the impulses they normally carry is shown by arrows, and the names of some of the parts they supply are mentioned. In B, both nerves are cut through. The degenerated portions are represented by discontinuous lines. In C, the union described in the text has been accomplished, and stimulation at the point *a'* now produces the same results as were in the intact nerves (A) produced by stimulation at *a*.

same throughout. So the nerve impulse is always the same sort of molecular disturbance; if it is made, as in the experiment just described, to go by a wrong channel, it produces just the same results as though the impulse had reached its destination by the usual channel.

Effects of Stimulation.—Excitability and conductivity are appreciably influenced by stimulation, and Waller, who first made the suggestion, considered the effect to be due to the small amount of CO_2 produced. Until 0.015 of a second after stimulation the excitability of the nerve is decreased; indeed, for 0.003 sec. it will not respond at all (absolute refractory period). The excitability returns to normal or slightly above, but later there is a period of subnormal responsivity corresponding to the period of positive after-potential. This period is held by Gasser to explain the

phenomenon of inhibition and to be fundamental to the normal activity of the nervous system.

These facts in relation to excitability give us an idea of the maximum number of impulses which can pass along a nerve in a given time.

The *relative absence of fatigue* in a nerve, as in the heart, is probably due to the fact that it is not acting continuously but intermittently, and during the resting period, although this is extremely short, it is able to recover. It is interesting to note that, as would be expected from the large heat production, crab nerve is fatigued comparatively quickly (Hill). An experiment to demonstrate the relative unfatigability of nerve is given on p. 71.

This is not to say that other nerves are absolutely unfatigable. After prolonged stimulation a diminished irritability, reduced current of action, and increased refractory phase is obtainable, but in spite of these changes a nerve will still continue to conduct. It is as if there was some form of adaptation to fatigue.

The Nature of the Nerve Impulse.

When a nerve is stimulated the change produced in it is known as the nervous impulse: this excitatory process travels along the nerve and the propagation of the change is evident from the effect which follows, *e.g.* sensation, secretion, movement, but the nature of the change produced in or on the nerve itself is, like the intimate nature of muscle contraction, unknown.

It is, however, clear that, while there may be several superficial resemblances, a nerve is not merely a conductor of impulses, as a wire is of an electric current. The most important fact which makes a simple physical view difficult is that conduction in a nerve apparently depends on some vital activity, as it is abolished by anæsthetics. Moreover, the velocity of the nerve impulse, which is much less than that of an electric current, is influenced by change of temperature much more than a purely physical process would be (Maxwell, Keith Lucas).

It is important to emphasise that whatever the nature of the nerve impulse, the impulse is self-propagating, somewhat like the combustion in a train of gunpowder when ignited, although admittedly this convenient analogy is a very crude and erroneous one. Adrian has shown that if the conductivity of a nerve be locally damped down by placing a segment in a chamber of alcohol vapour, the impulse as soon as it reaches an undamped region flares up to its original strength as judged by its effect on the attached muscle or the extent of the electrical change set up (see below). It was originally thought that there was a gradual fading out of the impulse (conduction

with decrement) in the chamber, but it has now been shown that the damping is more abrupt (Kato, Davis, Forbes). Nerve conduction is abolished by freezing, by CO_2 and anæsthetic vapours, and by the passage of a constant current which presumably acts by setting up a movement of ions in a given direction.

It may also be blocked temporarily by gentle compression. This occurs sometimes as a result of tumours. In this connection, too, it is interesting to note that in a mixed nerve, motor fibres are more easily blocked than sensory. The fibres carrying pressure, cold, heat, and pain are blocked in that order. Chemical agents block in the reverse order. No doubt this is a matter of the different sizes of fibres.

The Changes which occur in Nerve during Activity.—These are electrical, chemical, and thermal, as in muscle.

The Electrical Change.—The current of action of nerve like that of muscle may be demonstrated by means of non-polarisable electrodes and a string galvanometer or cathode ray oscillograph after amplification by means of thermionic valves. Although at first simply a curiosity this change of electrical potential has been shown to be of more interest than at first thought. It is propagated at the same rate as the impulse, it is present in every nerve that conducts and is depressed by all agents which depress conduction. Its size may be taken to represent strictly the size of the impulse; indeed, so closely related is the change of potential to the impulse that there are many who believe that the former is indeed the nerve impulse itself. (See "The Nature of the Nerve Impulse.") Our knowledge of this subject we owe largely to the studies of Erlanger of St Louis, U.S.A., and Gasser of the Rockefeller Institute, who have shown that it gives rise to a wave which has a characteristic and immutable shape.

If one electrode is placed on the nerve and the other earthed and the nerve stimulated by applying to it a hot wire, to avoid electrical complication, an initial abrupt and large negative wave, which may be as much as from 25 to 50 millivolts, is recorded. This is known as the spike. It not only falls off rapidly but is followed by waves of negative and positive after potential. Its general form is not unlike that already figured for the current of action of muscle but the spike is sharper and larger (see fig. 22).

While it is clear that conduction of an impulse depends on the state of a vital structure, the nerve, there is increasing evidence that the impulse is itself a physical process.

Lillie has made an interesting model which in many ways imitates the conduction of a nerve impulse. If a piece of iron wire is placed in a solution of nitric acid with a specific gravity over 1.2, a thin film of oxide is formed on its surface which protects it. If now

the wire is "stimulated" at one end by the usual means, it becomes black at that place and effervesces for a short period. The activation propagates itself to the other end like a nerve impulse and the wire cannot be activated again for a given space of time, *i.e.* it has a refractory period and gives all the phenomena which are found in nerve, except of course its vital reaction, *e.g.* to drugs. A constant current has the same effect as on a nerve. If a circle of wire of sufficient length is used, the wire goes into a continuous cyclic disturbance which is most fascinating.

Lillie's experiment has given rise to a number of theories as to the nature of the impulse of which by far the most important is the view that it is a change of potential due to depolarisation which passes down the surface of the axis-cylinder. If, for example, the surface of the nerve-fibre at rest consisted of a monomolecular film of fatty acid and was positively charged while its interior was maintained negative by the oxidation processes going on—a state commonly found in living things—it would be conceivable that any physical disturbance of the surface, such as that brought about by stimulation, would bring about a depolarisation or equalisation of potential between the surface and the interior which would spread to the adjacent polarised region. An alternative view is that the current of action, once set up, acts as a stimulus to adjacent parts after the manner of a train of gunpowder.

The subject is a fascinating one and its importance is obvious although a true explanation is not yet available. It will be seen that any of the physical hypotheses include the self-propagating nature of the impulse.

Chemical Changes.—The idea that there was definite metabolism in nerve was first advanced by Waller, and all subsequent work has confirmed his suggestion. Indeed it has been shown that resting nerve, if placed in suitable solutions, utilises carbohydrate and fat, while the giving off of ammonia indicates protein metabolism also. It has been shown that small amounts of carbon dioxide are produced and that for continued activity oxygen is necessary. Like muscle, nerve can function for a time in the absence of oxygen, and although, for nerve, this period is considerable it is not unlimited. If the nerve be frequently stimulated in an atmosphere of CO_2 or an inert gas, it ceases to conduct; but it recovers with extreme rapidity when again exposed to oxygen or air. During the inactive period not only the physiological response, *e.g.* the contraction of muscle, disappears, but also the electrical change. Both, however, return with the return of the other signs of activity. Anaesthetics, which dissolve in the lipides, of which the nerve is largely composed, appear to act by stopping oxidative processes.

Thermal Changes.—It is only recently that it has been possible

to demonstrate the small amount of heat produced by nerve; its presence had been assumed because of the chemical changes. A. V. Hill succeeded in doing this, using a thermopile with 300 constantan (an alloy of copper and nickel) and silver junctions which is capable of recording changes of less than a millionth of a degree of temperature. The effect is intensified by placing a bundle of nerves on the thermopile and utilising an extremely delicate galvanometer system. He found evidence of heat production, not only during the conduction of the impulse but also during the recovery period, as in muscle. The heat production in some of the nerves of crabs has been found to be relatively large.

The Humoral Transmission of the Nerve Impulse.

The evidence is now very complete that nerves do not act on tissues directly, but through the agency of chemical mediators, especially acetyl-choline.

The chemical nature of this substance and its general activity is given in a separate section (see Acetyl-choline).

The first suggestion of the occurrence of such humoral transmission came from Loewi, who found that, when the heart is slowed by stimulation of the vagus, a chemical substance is produced which will slow another heart. This is found to be due to the liberation of **acetyl-choline**, a substance long known to slow the heart and to dilate blood-vessels. Its chemistry is discussed in a separate section. The exact conditions under which the fluid leaving a slowed frog's heart perfused with saline can be caused to slow a second heart have been worked out by Bain, who has shown that the exact hydrogen-ion concentration of the perfusion fluid is very important, otherwise the acetyl-choline is destroyed. The action of the acetyl-choline is prevented by the drug atropine, but it can be shown that it is still produced, for if the atropine is painted on the first heart only the second heart still slows when the nerve to the first is stimulated although the first does not. The drug eserine (physostigmine), on the other hand, prevents the destruction of the acetyl-choline and prolongs its action. This action of eserine in assisting the action of choline had been discovered by Thomas Fraser many years before in his studies of drugs in pursuit of pure knowledge, but at the time it seemed of no importance.

Vasodilatation by nerves has also been shown to be similarly produced. Lewis has put forward evidence that the blisters of herpes (shingles), a condition due to inflammation of the posterior root ganglia, are caused by the production of a histamine-like, "H" substance in the skin (see Capillaries); while Dale and Gaddum have recently found that the vasodilatation produced by

stimulation of vasodilator nerves is due to acetyl-choline, and they explain the absence of action of atropine in such vasodilatation by the suggestion that the atropine cannot reach the acetyl-choline before it stimulates the muscle.

It has since been shown by Dale and his co-workers (Brown and Feldberg, 1935) that acetyl-choline is produced at the nerve-endings of the ordinary somatic nerves, but hitherto its very rapid destruction in the blood caused it to escape notice. Attention was drawn to the possibility of its importance in relation to somatic nerves by the treatment of the disease myasthenia gravis with

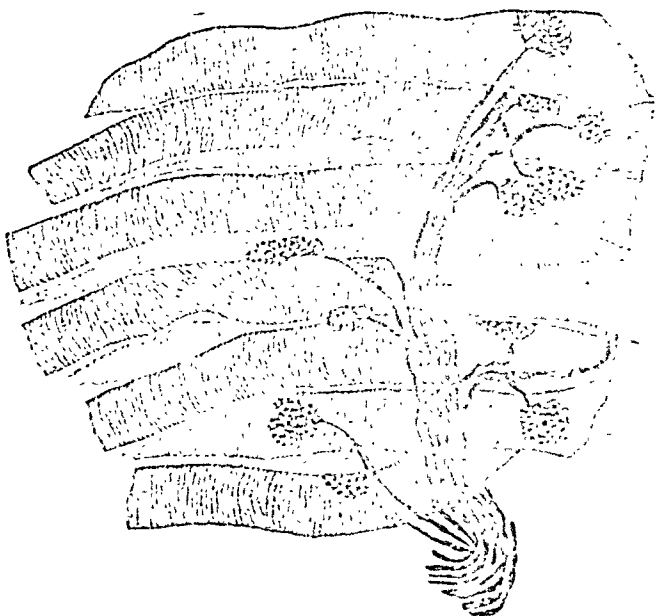


FIG. 85.—Motor end-plates; chloride of gold preparation to show the axis-cylinders and their final ramifications of fibrillæ. $\times 170$. (Szymonowicz.)

prostigmine* (Walker). Patients suffering from this fatal disease may be too weak to feed themselves, but the injection of prostigmine renders them almost normal for a few hours. Dale with his colleagues showed that the injection of acetyl-choline into the blood-vessel supplying a muscle causes it to twitch just like the stimulation of its nerves. In order to produce this result, however, the circulation must be arrested temporarily and the injection made at close range. Also eserine, which prevents the destruction of acetyl-choline, greatly enhances the response to a single motor nerve volley, while the drug has no such effect on the response of denervated muscle to direct stimulation.

Evidence points to the acetyl-choline being liberated in the

* Prostigmine is a substance like eserine. The effects of acetyl-choline generally are augmented by minute doses of adrenaline.

region of the motor nerve-endings or plates which have a peculiar structure.

The nerve-fibre branches two or three times, and each branch goes to a muscle-fibre. Here the neurolemma becomes continuous with the sarcolemma, the medullary sheath stops short, and the axis cylinder breaks up into terminal ramifications.

It now seems likely that many of the phenomena which we have noted in relation to muscle are explicable as due to the accumulation of acetyl-choline at the nerve-endings, especially the effects of summation and the genesis of tetanus.

Some sympathetic nerves have also been shown to liberate a chemical substance **sympathin**, which has an action almost identical with that of adrenaline and the opposite action to acetyl-choline.

Finkleman demonstrated that when a piece of intestine contracting rhythmically in a trickle of oxygenated saline is inhibited by stimulating its attached splanchnic nerve, there passes into the saline a chemical substance like adrenaline, which inhibits the movements of another piece of intestine. Later on, Cannon brought forward evidence to show that, when blood-vessels are caused to constrict by nerves, a similar substance is produced which acts like adrenaline on the heart.

Humoral transmission may also occur within the nervous system itself, for if fluid is passed through the superior cervical ganglion and the sympathetic stimulated, acetyl-choline is released into the perfusion fluid. It has long been known that sympathetic ganglia were particularly rich in choline. Potassium is also released, but the significance of the fact is not yet understood and the whole subject is much debated (see Eccles). The release probably takes place at synapses. These are discussed in a separate section later.

Velocity of a Nerve Impulse.

The velocity of a nerve impulse may be measured, in motor nerves, by the method first used by Helmholtz: a muscle-nerve preparation is made with as long a nerve as possible; the nerve is stimulated, first as near to the muscle and then as far from the muscle, as possible. The moment of stimulation and the moment of commencing contraction are recorded by muscle-tracings on a rapidly moving surface provided with a time-tracing. When the nerve is stimulated at a distance from the muscle, the contraction begins later than it does after the first stimulation, and the difference between the two is the time occupied in the passage of the impulse along the intervening piece of nerve, the length of which is known.

The most accurate method is that of Bernstein, in which the

electrical change is the indication of the impulse. A stimulus is applied to one end of a long nerve, and the change in the electrical condition of the nerve is recorded by a galvanometer connected to the other end of the nerve. The time between the application of the stimulus and the galvanometric reply is measured.

In the frog, for instance, at ordinary room-temperature the velocity averages **27 metres per second**. In warm-blooded animals it is **90-120 metres per second**.

By using the cathode-ray oscillograph, Erlanger, Gasser and their co-workers have been able to study different fibres of nerves in more detail. Three groups have been differentiated in the frog.

Group A fibres have velocities of 30-90 metres per second. They carry impulses to and from the muscles, impulses from the skin, sensations of touch and temperature, and impulses of the para-sympathetic.

Group B have slower rates, 10-20 metres per second. They are sympathetic and convey impulses to the blood-vessels and glands.

Group C have still slower rates, 0.3-1.6 metres per second. These are concerned probably with crude sensations. Pain impulses are apparently carried by all fibres.

This has been discovered by stimulating a long nerve and finding that the impulses set up reach a point some distance away at different times (Gasser, Erlanger and Bishop).

Histological investigations show that the rates of conduction are proportional to the size of the fibres, the larger fibres conducting more rapidly than the smaller.

Afferent impulses, as measured by Gasser, travel at about a third of the rate of efferent impulses in the same reflex arc.

Direction of a Nerve Impulse.

Nerve impulses are normally conducted in only one direction: in efferent nerves from, in afferent nerves to, the nerve-centres. But experiments indicate that conduction may under certain conditions take place in both directions. Thus, in the galvanometer experiment just described, if the nerve is stimulated in the middle instead of at one end, the electrical change (the evidence of an impulse) is found to be conducted towards both ends of the nerve.

A nerve impulse can, however, only pass in one direction across a synapse, that is only from axon to dendron. How this may be brought about is a matter of debate. It is possible that a chemical mediation is liberated at the endings of the axons which in many instances are button-like. The subject is discussed later in relation to the functions of the synapse.

The Effect of Electric Currents on Excitability and Con-

ductivity.—These effects are of some interest as they may throw a light on the problem of the nature of the nerve impulse.

If a constant current at about 2 volts is passed through a nerve and the excitability of the nerve tested by placing a pair of stimulating electrodes close to the positive (the anode) and to the negative (the kathode) wires, it is found that in the region of the anode the nerve is unexcitable, while in that of the kathode it is hyperexcitable. These conditions are known as *anelectrotonus* and *katelectrotonus* respectively. If then a constant current is passed through a nerve the nerve ceases to conduct (Bernstein) because of the area of anelectrotonus at the anode. Use is commonly made of this fact in physiological experiments as such a nerve-block is equivalent to nerve section with the advantage that it is only temporary.

This effect on a nerve must not be confused with the momentary stimulation of a nerve which may occur the moment the circuit is made or broken. At the make the stimulating electrode is the kathode, but at the break the stimulating electrode is the anode, facts of some importance in relation to reaction of degeneration (see below) in which the excitability is altered.

Reaction of Degeneration.—When the nerve to a muscle becomes injured or impaired the excitability of the muscle is for a short period increased but later exhibits certain changes which appear to indicate a reduced excitability.

When the nutrition of the nerves is impaired, much stronger currents of both the induced and constant kinds are necessary to evoke muscular contractions than in the normal state. When the nerves are completely *degenerated* (when, for instance, they are cut off from the spinal cord, or when the cells in the cord from which they originate are themselves degenerated, as in infantile paralysis) no muscular contraction can be obtained on stimulating the nerves even with the strongest currents.

When the motor nerve is degenerated and will not respond to any form of electrical stimulation, the muscle also loses all its power of response to currents of very short duration such as those produced by an induction coil. The nerve-degeneration is accompanied by changes in the nutrition of the muscle-fibres, as is evidenced by their rapid wasting, and their failure also to respond to rapid induced currents. A weaker constant current, however, stimulates the muscle more than in the normal state, because the muscle-fibres themselves are in a state of irritable weakness, but the contraction is propagated more slowly than when the nerve-fibres are intact. There is, moreover, a qualitative as well as a quantitative change. In health the first contraction to occur on gradually increasing the strength of the current is at the negative pole, when the circuit is

closed (Pflüger's law), and a stronger current is required before closure-contraction occurs at the positive pole. But in the morbid state we are discussing, closure-contraction may occur at the positive pole more readily than at the negative pole, *i.e.*, A.C.C. is greater than K.C.C.*

The reaction of degeneration is of considerable importance in medical and surgical diagnosis as it is a convenient objective method of demonstrating whether or not the nerve supply to a muscle is intact. The sluggish reaction to a constant current is specially characteristic of degeneration which does not appear for some time after voluntary movement is lost. These changes are developed after a week or ten days, but after a longer period of months the muscles lose their power of contracting altogether. Gradually the muscles themselves degenerate and waste away.

Fatigue.

If the muscle of a nerve-muscle preparation be stimulated frequently, the muscular contractions become more prolonged, smaller in extent, and finally cease altogether. This can be demonstrated by making the muscle write a curve with every revolution of a recording cylinder, until it ceases to contract altogether owing to fatigue. At first the contractions improve, each being a little higher than the preceding; this is due to the *beneficial effect of contraction*. Then the contractions get less and less. But what is most noticeable is that the curves are much more prolonged: the latent period is longer, the period of contraction longer, and the period of relaxation very much longer. This condition is known as *contracture*, and the original base-line may not be reached by the time the next stimulus arrives. In the last stages of fatigue, contracture passes off. Contracture is often absent in fatigue of mammalian muscle.

Fatigue of muscle stimulated directly is due to the consumption of the substances available for the supply of energy in the muscle, but more particularly to the accumulation of waste products of contraction; of these sarcolactic acid is the most important. Fatigue may be artificially induced in a muscle by supplying it with a weak solution of lactic acid, and may then be removed by washing out the muscle with salt solution containing a minute trace of alkali. If the muscle is in the body, the blood-stream washes away part of the accumulation of acid products; the remainder is oxidised or resynthesised and fatigue passes off.

When a nerve-muscle preparation has been fatigued by stimulation through the nerve it is found that the muscle will still contract

A.C.C. = Anodal closing contraction. K.C.C. = Kathodal closing contraction.

if stimulated directly, and this raises the question whether the nerve or the nerve-ending is the seat of the fatigue. That the nerve is not fatigued may be shown by the following experiment. A temporary block is applied to the nerve between the point of stimulation and the muscle. For blocking a piece of ice or a galvanic current (see p. 63) may be used. The nerve is now stimulated for a period much longer than that which would be necessary to cause fatigue if contraction were occurring. During such a period the nerve, if fatigable, must have become fatigued, but it is found that immediately the block is removed the nerve conducts quite normally.

From the above experiments it has been concluded that, since neither the nerve nor the muscle have been fatigued, the **seat of fatigue** must be in the region of the nerve-endings, and possibly due to an exhaustion of a humoral transmitter or its precursor. There are still many facts regarding fatigue which are not understood, but the simple fact remains that the muscle can be excited by stimuli such as are produced by an ordinary induction coil. We are thus reminded that the impulse which passes down a nerve may, for reasons indicated on p. 62, bear no relation to the strength of the stimulus applied to the nerve.

The action of curari, the South American arrow poison, is now believed to be due to similar change in the excitability of the muscles so that they cannot be stimulated through their motor nerves. When the muscles of respiration become affected and cease to act death occurs.

Fatigue of Voluntary Movement.

The foregoing suggests that local poisoning is responsible for fatigue, and in support of this, Mosso showed that the blood of a fatigued animal caused fatigue if injected into the blood of another.

It has, however, been shown that if the circulation to a part is cut off the liability to fatigue is not so great as would be expected (Reid). Other factors must be considered.

By the use of the ergograph (Mosso, Waller), it has been shown that the state of the brain and central nervous system generally is an important-factor in fatigue.

One of the most striking of Mosso's experiments illustrates in a very forcible manner the fact that the central nervous system is more easily fatigued than muscle. A person goes on lifting a weight as shown in fig. 36A until, under the influence of the will, he is unable to raise it any more. If then, without waiting for fatigue to pass off, the nerves going to the finger muscles are stimulated artificially by induction shocks, the muscles once more enter into vigorous contraction.

It may be that the "fatigue" which occurs in central synapses

is a result of the formation of fatigue products locally or the exhaustion of central cells. This has been supported by the finding that in fatigue the Nissl granules of the nerve-cells which usually stain well with methylene blue, are absent or are represented by a diffuse blue haze (chromatolysis). It has, however, been suggested (Reid) that something of the nature of a central inhibition results from impulses which pass up from the active muscles themselves. It appears that normally we are capable of using only a certain proportion of the muscle-fibres at one time, because inhibitory impulses

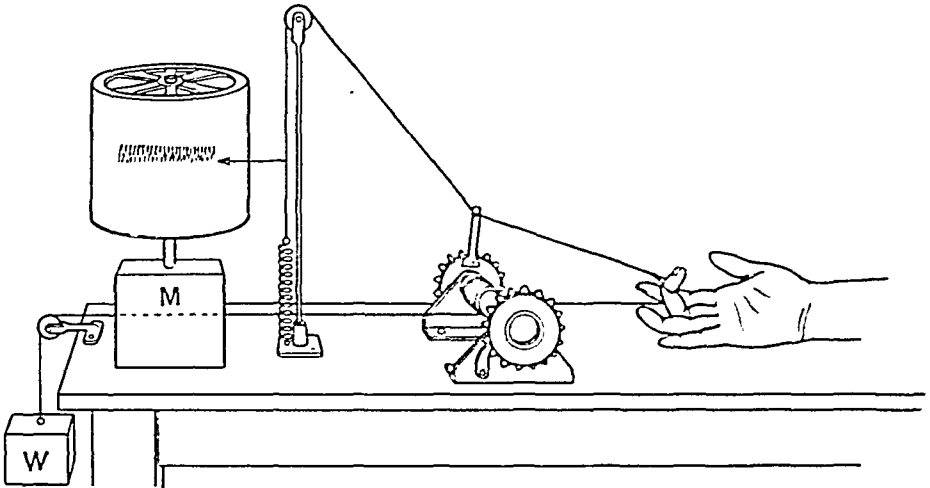


FIG. 26A.—A simple ergograph. The subject pulls with his finger at a rate set by a metronome. The work done may be calculated from the record on the drum or by the height to which the weight (W) is raised (see next figure). Two bicycle free-wheel mechanisms make robust ratchets.

are set up by the pressure on the sensory nerve-endings, the spindles of the muscles, and pass into the central nervous system (Denny Brown). The excessive strength which can be exercised by a madman or individual under severe stress may in part be due to his bringing into use more fibres than can be used normally. This lengthening reflex which presumably prevents muscles from being torn from the bones can be demonstrated in a cat whose cerebrum has been removed (see Decerebrate Rigidity).

The Sensation of Pain in Muscle.—The pain which results when a muscle is exercised, especially if its blood supply is defective, has been specially studied by Lewis because it throws light on the very intense pain which occurs when the arteries to the heart are occluded. This pain is one of the most severe known to man. It has been found that the intensity and duration of pain, when produced in the arm of man, are increased if the blood supply is occluded by a sphygmomanometer cuff. It is therefore suggested that a chemical substance is produced (Pain Substance) which

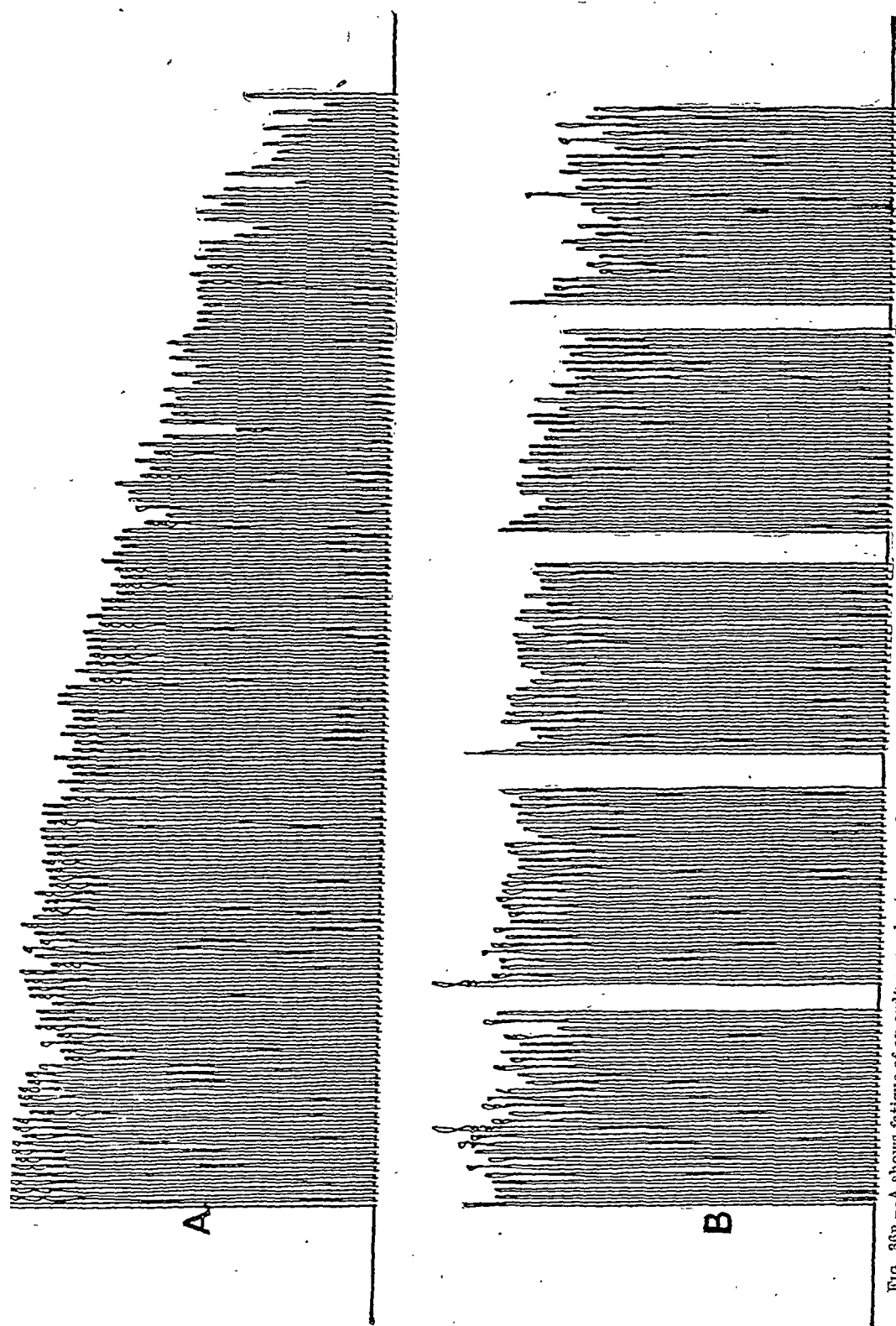


Fig. 36n.—A shows fatigue of an ordinary voluntary muscle of a finger, doing work on an ergograph at the rate of 48 contractions per minute. In B the subject worked for the same length of time—three minutes—but took four rest periods of five seconds each. In A the amount of work done was 1.80 kilogramme-metres. In B the amount of work done was 2.28 kilogramme-metres. (Whittles.)

stimulates the sensory nerve-endings. It may be lactic acid which, as we have seen, is at least partly responsible for local fatigue. The subject is discussed later in regard to that of Sensation.

Rest Pauses.—It may be shown on an isolated muscle or by means of the ergograph that it is not economical to fatigue a muscle to its limit and that to get the maximum work out of it in a given time there should be rest pauses. The pauses should, as far as possible, be evenly distributed.

A good example is quoted by Myers. If in an ergograph experiment the finger makes 30 contractions in 60 seconds with a certain load, two hours' rest is necessary for complete recovery. If, on the other hand, the finger makes 15 contractions in 30 seconds with the same load a rest of only half an hour is necessary. Hence in a two-hour period of work the second arrangement would give double the output of work.

These facts which were extensively studied in munition works especially by Vernon from 1914 to 1918 have a wide application to work generally, as they not only give more leisure to the worker but increase the quantity and quality of the work done. Experiments on the learning of poetry by students, and on rats learning to get out of a maze, suggest that it is probable that the necessity for rest pauses applies to mental work also.

General Fatigue.

In addition to the fatigue described above there is a fatigue which depends on more general states such as the total amount of energy in the body. It is possible, too, that fatigue products may circulate in the blood, for we have seen that local fatigue is the result in part of the accumulation of such products which are normally washed away in the blood stream. We know, too, that in exercise lactic acid passes into the blood stream and is excreted in the urine as lactate. Workers on the subject of industrial fatigue have shown that a great deal can be done to eliminate this by the avoidance of all unnecessary movements, by reducing the total amount of muscle used, *e.g.* by not using the large muscles of the trunk and legs and by making continued smooth movements instead of a series of new movements which waste energy in overcoming inertia and viscosity.

Many mental factors also tend to affect fatigue, notably incentive, boredom and general conditions of work, especially the temperature and humidity of the air. Most are familiar with the bracing effects of dry, cool air and the enervating action of a hot, moist atmosphere.

The factor which is really important is the cooling power of the air which is determined by the kata-thermometer introduced

by Leonard Hill. This is essentially an alcohol thermometer. It is heated to 100° F. and the observer takes the time for it to fall to 95° . It may be used like a wet-bulb thermometer by covering it with a wet cloth. The cooling power of the air depends on its temperature, humidity, and movement. A gentle breeze of 100 feet per minute with a temperature of 72° F. will cool as much as a temperature of 60° will if there is no air movement. Hence the power of draughts in producing chilling of the body, and the benefit of fans. The optimum working temperature, as judged by the accident incidence in factories, appears to be from 60° to 65° F.

CHAPTER IX

THE AUTONOMIC NERVOUS SYSTEM

STUDENTS unfamiliar with elementary anatomy should read the section on the spinal cord before reading this chapter.

It must be clearly understood that the autonomic nervous system is part of the general nervous system with which it works in close harmony. It is described separately, partly for purposes of convenience and partly because it controls certain automatic bodily activities, *e.g.* the circulation and digestion, over which we have no voluntary control, which it is common to describe before the nervous system as a whole. Anatomically the system is peculiar in that the neurones of which it is composed have synaptic junctions in ganglia outside the central nervous system.

The elucidation of the autonomic nervous system we owe to Gaskell (1915) who first realised its general plan, and to Langley who, also in Cambridge, worked out a large amount of its detail. Also certain of its activities may be initiated by the injection of certain drugs, or may be paralysed by them in a way not possible with the rest of the nervous system.

The autonomic nervous system is divided into at least two parts which are anatomically, pharmacologically, and physiologically more or less distinct. This distinction is convenient, but it must be understood that there is no real distinction in regard to function.

1. **The sympathetic** which arises from the first thoracic to the third lumbar anterior nerve-roots of the spinal cord.

2. **The parasympathetic** arises in connection with certain cranial nerves, the thoracic nerves,* and second, third, and fourth sacral anterior roots of the spinal cord.

In addition some authors (*e.g.* Langley, Gaskell) distinguish the **enteric system** which consists of ganglia and plexuses in the wall of the intestine, but these are intimately associated with the sympathetic and parasympathetic, particularly the latter.

(A) **THE SYMPATHETIC SYSTEM.** It must be understood that little more than the origin of this system has so far been established. There is much evidence that the controlling fibres pass down from the brain, probably from the hypothalamic region. In the spinal cord they have been found passing down in the lateral columns. From their origin in the lateral horn of the spinal cord the axons leave by way of the anterior roots of the spinal nerves from the first thoracic to the third lumbar segments inclusive. The axons separate from the mixed nerves as the **white rami**

* Prior to inclusion of these nerves in the parasympathetic, this group was known as the **cranio-sacral autonomic**.

communicantes and join a chain of ganglia, or collections of nerve-cells, the lateral chain, situated on each side of the vertebral column. These ganglia correspond roughly to the spinal segments from the coccygeal, or lowest, ganglion upwards, and are joined together by connecting fibres. In the upper part, however, the ganglia corresponding to the upper four thoracic roots are fused to form the large stellate ganglion and the upper four cervical are fused to form the superior cervical ganglion. In man, the lower cervical ganglia form the middle and inferior cervical ganglia, but in many animals, *e.g.* the cat and dog, the latter is fused with the stellate.

From the ganglionic chain fibres are distributed in two main directions (see fig. 39).

1. *To the collateral or prevertebral ganglia.* These are the coeliac from which the coeliac plexus takes origin, the superior mesenteric, and the inferior mesenteric from which the hypogastric nerves arise. From these outlying ganglia fibres pass to the terminal ganglia and nerve plexuses in connection with thoracic, abdominal, and pelvic viscera.

2. *To the spinal nerves.* These are known as the **grey rami** because of their colour. They pass with the spinal nerves to structures such as blood-vessels, muscles of the hairs, and sweat glands. It will be noticed that, although the white rami arise only from certain spinal roots, the grey rami return to each of the spinal nerves from the nearest ganglion of the lateral chain.

The impulses that pass to the involuntary musculature of the body arise in the central nervous system, and travel to the ganglia of the autonomic system by means of fine medullated nerve-fibres; the diameter of these fibres varies from 1.8 to 3.6 μ ; the fibres therefore contrast with the motor fibres which pass to voluntary muscles, the diameter of these being 14 to 19 μ (see fig. 35, p. 66). There is a further contrast between them: the motor fibres to voluntary muscles pass uninterruptedly from the central nervous system until they terminate in the end-plates of the muscles. The autonomic fibres, on the other hand, terminate by arborising round cells in one or other of the autonomic ganglia, and from the ganglion cells a fresh relay of nerve-fibres carries on the impulse to the involuntary muscles. There is thus an extra cell-station or synaptic junction altogether outside the central nervous system. The autonomic path, in other words, consists of two neurones: one from the central nervous system to the ganglion, and a second from the ganglion to the peripheral tissue. The first axon is termed the *pre-ganglionic fibre*; the second, the *post-ganglionic fibre*. The pre-ganglionic fibres are medullated ones, and the post-ganglionic fibres are usually non-medullated, but there are exceptions to this rule.

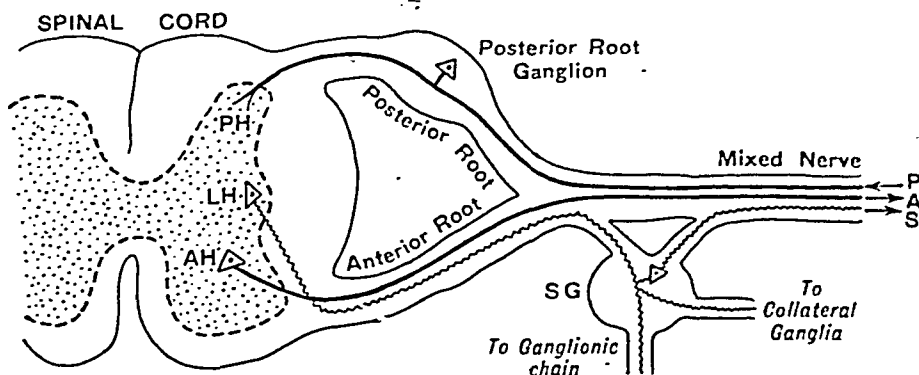


FIG. 37.—Diagram of the autonomic path in the spinal region. AH, anterior cornual cell giving rise to a large motor nerve-fibre which is distributed to voluntary muscle. LH, a small cell of the intermedio-lateral tract giving rise to a small medullated nerve-fibre which leaves the cord by an anterior root, and leaves the anterior root by the white ramus; it terminates by arborising round cells in a ganglion of the sympathetic chain. From these cells fresh non-medullated axons continue the impulse, and return to the spinal nerve by the grey ramus, being finally distributed to involuntary muscle-fibres. To complete the diagram, a posterior root-fibre is also shown with its parent cell in a spinal ganglion. Post-ganglionic fibres arising in the lateral ganglion and passing to outlying ganglia or organs are not shown.

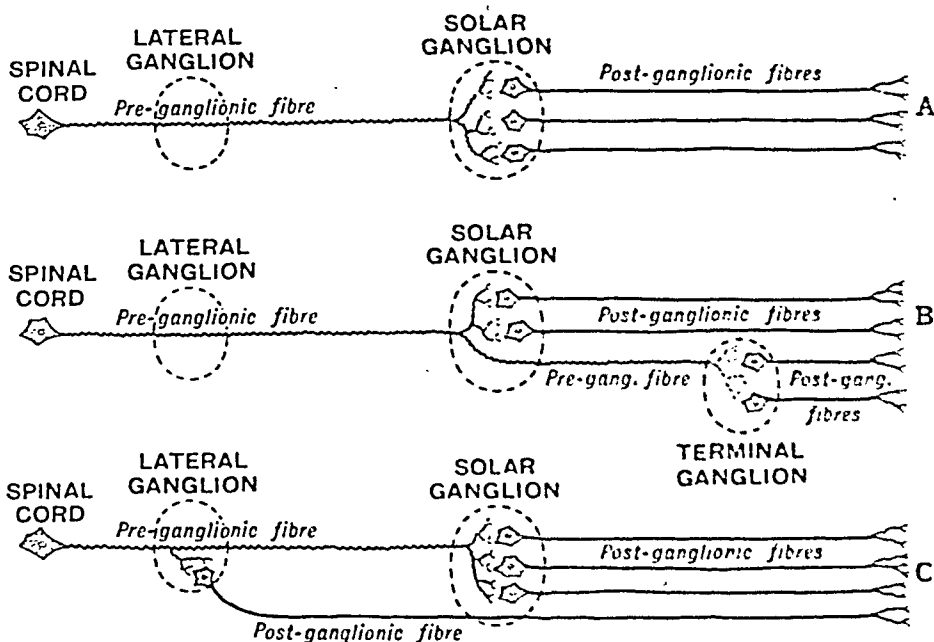


FIG. 38.—Arrangement of pre- and post-ganglionic fibres in splanchnic and inferior splanchnic nerves. (After Langley.)

The general arrangement of such nerves is represented in fig. 37.

The cell-station of any particular pre-ganglionic fibre is not necessarily situated in the first ganglion to which it passes; the fibres of the white ramus communicans of the second thoracic nerve, for instance, do not all have their cell-stations in the second thoracic ganglion, but may pass upwards or downwards in the chain to a more or less distant ganglion before they terminate by arborising round its cells. It therefore follows that fibres that leave any given spinal nerve by its white ramus do not necessarily return as post-ganglionic fibres by the grey ramus to the same spinal nerve, although, for the sake of simplifying the diagram, they are represented as doing so in fig. 37.

Furthermore, there are many fibres of the white rami which enter the lateral chain of ganglia and pass through it without communicating with its cells at all, and never return to the spinal nerves by grey rami. They pass out of the lateral chain to either collateral or even terminal ganglia before reaching their cell-stations, whence the post-ganglionic fibres emerge. This is the case for the sympathetic supply of the blood-vessels and involuntary muscle fibres of the thoracic, abdominal, and pelvic viscera, and is therefore true for such important nerves as the cardiac accelerators and the splanchnics.

Fig. 38 shows the course of the splanchnic fibres, and will help the student to grasp this method of distribution.

The great majority are arranged as in A, that is to say, they have their cell-stations in the solar [coeliac] ganglion. Comparatively few are arranged as in B, where some fibres do not reach their cell-stations until they arrive at the terminal ganglion situated in the walls of the viscus (for instance, the pancreas) to which they are distributed. A few possibly are arranged as in C, with a cell-station for some of their branches in the lateral sympathetic chain.

It will be noticed that if any post-ganglionic fibre is traced backwards, there is one and only one cell-station between the central nervous system and the ultimate distribution of the nerve-fibres.

Elucidation of these facts we owe largely to the use of **the nicotine method** originally introduced by Langley and Dickinson, and employed later by Langley mainly in conjunction with H. K. Anderson.

Nicotine in small doses paralyses nerve-cells, but not nerve-fibres. It is still a matter of uncertainty whether the drug produces these effects on the nerve-cells themselves or on the terminal arborisations (synapses) of the fibres that surround them, or on receptive substances either in the cells or present at the synaptic junctions. But whichever of these views is correct, the main result is the same: a nervous impulse which reaches a ganglion by a pre-ganglionic fibre cannot

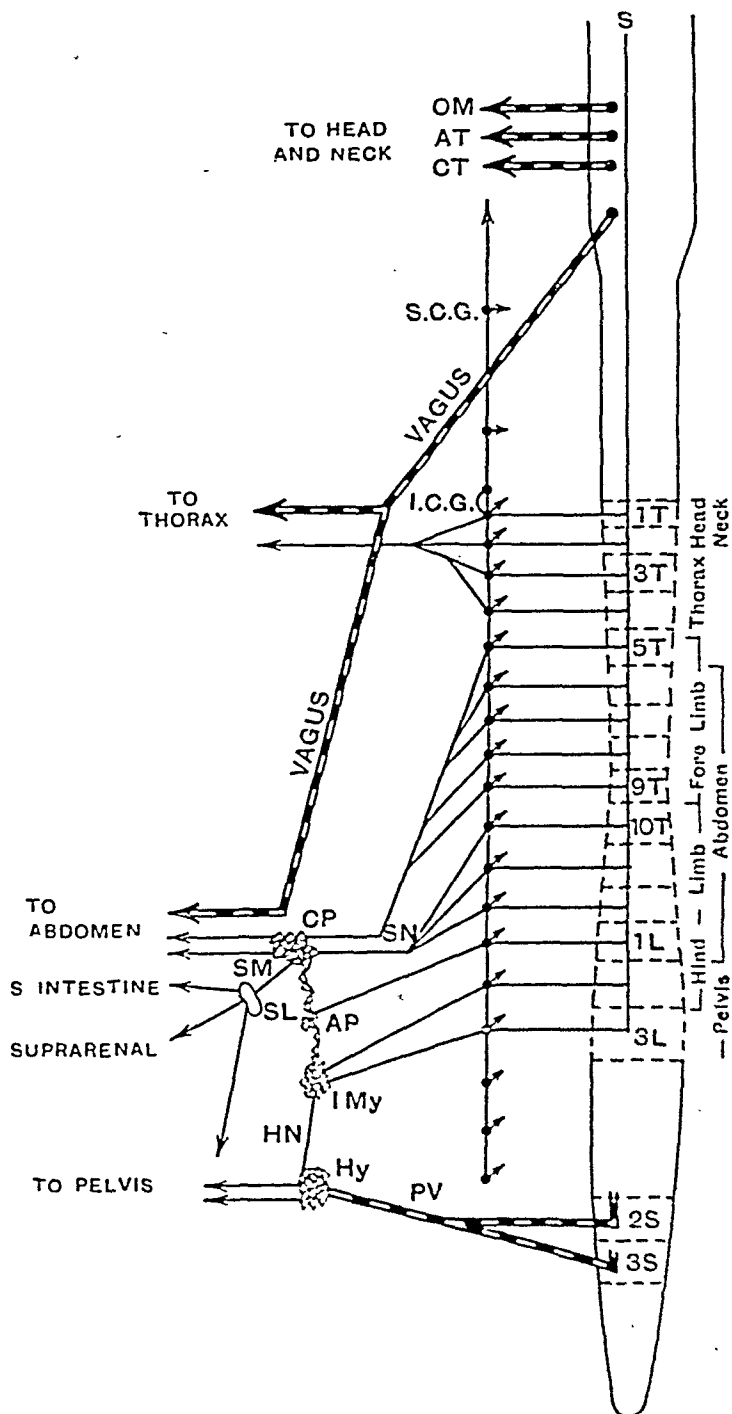


FIG. 39.—Diagram of the Autonomic Nervous System, showing its origin from the Central Nervous System. The small arrows from the ganglionic chain indicate branches to limbs, trunks, etc. Spinal parasympathetic fibres are not shown. OM, oculo motor; AT, auriculo temporal; CT, chorda tympani; S.C.G., sup. cervic. ganglion; I.C.G., inf. cervic. ganglion; CP, celiac plex.; SN, splanchnic nerves; SM, sup. mesenteric plex.; AP, aortic plex.; IMy, inf. mesenteric plex.; HN, hypogastric nerve; Hy, hypogastric plex.; PV, pelvic nerve; SL, celiac ganglion.

get across to the corresponding post-ganglionic fibres if the ganglion is painted with nicotine. Stimulation of the anterior nerve-roots, or of the white rami no longer produces movements of the involuntary muscle tissues, because the paralysed cell-stations act as blocks to the propagation of the impulses. If, however, post-ganglionic fibres are stimulated, the usual effects (for instance, constriction of blood-vessels, erection of the hairs, etc.) take place. The nicotine may be injected into the circulation or it may be painted over one or more ganglia: the latter causes a block only in those fibres which have their cell-stations in the particular ganglia. By patiently examining in this way all the ganglia in turn, stimulating the fibres that enter each and those that leave it, Langley and his colleagues, after years of work, were successful in localising the cell-stations on most of the autonomic paths in the body.

We shall, in later chapters, consider the sympathetic nerve supply of the individual organs, but it is convenient here to state the main course of the distribution of these nerves (see fig. 39).

The head and neck are supplied with fibres which arise from the upper two thoracic segments and the thorax from the upper five.

The abdomen gets fibres from the lower seven thoracic ganglia. The fibres form into two groups to form the splanchnic nerves which pass to the collateral ganglia and plexuses.

The remaining lumbar ganglia, which have white fibres, supply the lower abdomen and pelvis, and are distributed similarly. One bundle of fibres arising from the inferior mesenteric ganglion is known as the hypogastric nerve.

The plexus and the finer nerve-fibres commonly lie on the walls of blood-vessels along with which they are distributed to outlying organs, like the fibres which pass out with the spinal nerves.

The tissues supplied are blood-vessels, secretory glands, hairs, and the unstriated muscles of certain organs such as the intestine and spleen, whose functions are thereby correlated with the general requirements of the body.

(B) THE PARASYMPATHETIC. The parasympathetic consists of fibres which arise from certain cranial, spinal, and sacral nerves.

1. *Fibres which arise from the mid-brain.*—These emerge by the third nerve; the pre-ganglionic fibres pass to the ciliary ganglion; the post-ganglionic, arising from the cells of this ganglion, run in the short ciliary nerves to supply the intrinsic muscles of the eyeball (sphincter iridis and ciliary muscle).

2. *Fibres which arise from the medulla oblongata.*—These emerge by the following nerves:—

(a) Seventh and ninth nerves. These supply the blood-vessels with vasodilator fibres and also the secreting glands in the nose and mouth region. The ganglia on the course of these fibres are the

spheno-palatine, otic, submaxillary, and sublingual ganglia. Some of these fibres (for instance, those in the chorda tympani) get bound up with branches of the fifth nerve and are distributed with them.

(b) Tenth and eleventh nerves These are distributed by the branches of the tenth or vagus nerve to the œsophagus, stomach, and small intestine, to the bronchial muscles, to the heart, and to the gastric and pancreatic secretory mechanism. Here our knowledge of the localisation of the cell-stations is not so exact as it is in other parts; some of the fibres appear to have their cell-stations in the ganglion on the trunk of the vagus, but in many cases they do not become post-ganglionic until the terminal ganglia in the walls of the various organs mentioned are reached.

3. *The spinal fibres and vasodilator nerves.*—The knowledge that certain fine medullated fibres in the posterior spinal roots when stimulated cause vasodilatation we owe chiefly to Bayliss, although their presence had been noted by Stricker. These fibres have been called *antidromic* because their impulses pass out against the general afferent stream of the posterior roots. They have hitherto not been considered parasympathetic because their action, unlike that of other vasodilator nerves, is not abolished by atropine. They are, however, the reciprocals of the vasoconstrictor nerves. The fact that they really do belong to the parasympathetic system has recently been much emphasised by Kuré and his co-workers in Japan, who claim that these fibres have a motor action on the alimentary canal.* Their view is supported by the work of Dale and Gaddum which indicates that vasodilator nerves act like the vagus by producing acetyl-choline, but in such a way that the action is not prevented by atropine. Kuré suggests also that they exert a trophic function and that the degeneration of tissues and liability to infection such as is seen in bed-sores is due to the degeneration of these fibres. It is considered that some of these parasympathetic fibres join the splanchnics with which they are distributed.

4. *The sacral fibres.*—The pre-ganglionic fibres emerge in the white rami of the second, third, and fourth sacral nerves. They pass through the sacral ganglia of the lateral chain without forming connections with any cells there, and they pass on as the nervus erigens, or pelvic nerve, to join the pelvic plexus. The fibres of this nerve supply vasodilator fibres to the external generative organs (whence its name), to the rectum and anus, and motor fibres to the musculature of the descending colon and rectum; they have their cell-stations in the small scattered ganglia of the pelvic plexus, or in terminal ganglia in the walls of the viscera they supply.

The Enteric System and Terminal Ganglia.—This term refers to

* These experiments have not, however, been confirmed by independent observers.

the ganglia and network of fibres in the walls of the intestine (plexuses of Auerbach and of Meissner). These apparently act as local nerve centres controlling purely local activity, but there is reason to believe that the sympathetic, but especially the parasympathetic, bring about their intestinal effects through these plexuses. Other terminal ganglia are those in the walls of the heart, bladder, and other organs, but the evidence that these can act as local nerve centres is not convincing; they seem to act chiefly as cell-stations on the course of incoming fibres especially those of the vagus. (See Control of Intestine.)

General Function of the Autonomic Nervous System.—Every organ of the body over which we have no voluntary control appears to be supplied with two sets of fibres—from the sympathetic and the parasympathetic—which have opposite functions. The appreciation of this fact we owe largely to Gaskell, to whom, and to Langley, is due so much of our knowledge on the subject. In Gaskell's nomenclature the sympathetic or accelerator group of nerves is termed *katabolic*, as they are concerned with general increase of work and utilisation of energy in the various parts of the body; the parasympathetic group *anabolic*, as it is more intimately concerned with the processes which take place during bodily rest.

While the statement is generally true it would probably be better to say that, while the sympathetic provides for the work of to-day the parasympathetic provides for the work of to-morrow. For example in relation to the heart, it may be shown that the process of physical training which promotes the muscular efficiency of the heart increases parasympathetic activity, but during the performance of the exercise the sympathetic action is increased while parasympathetic action is decreased. The parasympathetic may then be looked upon as supplementing the action of the sympathetic in that it increases the range of the activity. It also sensitises the tissues to sympathetic activity.

The *sympathetic* may be looked upon as adapting the body to the needs of muscular activity, emotion, and to exposure to cold. By far its most important and certain functions are to increase the heart-rate and blood-pressure, to arrest the activities of the alimentary canal, and to mobilise glucose; while increased action of the *parasympathetic*, e.g. the vagus, causes slowing of the heart and increased activity, motor and secretory, of the alimentary canal and all its associated glands.

The sympathetic has also many other detailed functions which may be enumerated: it reduces fatigue, dilates the pupil and bronchi, causes the secretion of sweat, and brings about the erection of hairs. It constricts cutaneous and splanchnic vessels, but dilates muscle vessels.

Most of the actions of the sympathetic are also brought about by the injection of adrenaline into the blood-stream, and by the

accumulation of carbon dioxide in the body, and there is good reason to believe that in severe physical exercise the activities of the sympathetic, adrenaline, and carbon dioxide reinforce each other. The apparent object of such a mechanism is to make available for the active muscles a maximum amount of oxygen-carrying blood, at the temporary expense of those parts of the body whose activity is not immediately required, *e.g.* the alimentary canal. The sympathetic makes it possible for the body to use its already accumulated store of potential energy without having recourse to its immediate environment for anything but oxygen, which it cannot store to any appreciable extent but which is normally always available in the atmosphere.

The relationship of the sympathetic system to afferent impulses.—

As we have said, we must look upon the nervous system as acting reflexly. Our knowledge of this subject is as yet very imperfect, but it is important to note that there is much evidence that stimulation of afferent nerves, *e.g.* the production of pain in man, or stimulation in anæsthetised animals, causes sympathetic activity, *e.g.* dilatation of the pupil, acceleration of the heart, and constriction of blood-vessels. The fact suggests the possibility of a connection between the posterior root-fibres and the white rami. Such a connection is still further emphasised by the facts that the posterior roots, unlike the anterior roots, contain a very large number of small (autonomic) fibres, and that the lateral ganglia and the posterior root ganglia are developed from the same mass of cells on the neural crest of the embryo, from which also is developed the medulla of the suprarenal gland, the hormone of which, as we shall see, acts like the sympathetic.

The exact mechanisms by which the sympathetic is called into operation have not yet been fully elucidated, but it is evident that its activity is specially related to sensation and to afferent impulses which may not reach consciousness. The effect of sensory stimulation may be looked upon as reflex in nature via the posterior roots and the rami communicantes. It is interesting to note that, although anæsthesia may abolish the connection between the posterior and the anterior roots, between the posterior root and the white ramus the connection is unaffected. It seems most probable that all the actions of the sympathetic are essentially reflex and depend on afferent impulses which reach the system from the external environment or internal structures.

The relative importance of the sympathetic and parasympathetic.—

It is becoming increasingly certain that the exact importance of these systems differ in different species (Cannon, Heymans, Samaan). **Removal** of the whole of the sympathetic chain in dogs does not appear to make any material difference to the animals. The cat, how-

ever, is liable to collapse if it attempts any severe exercise, becomes emotionally distressed, or is exposed to extremes of temperature.

Section of the vagi (below the origin of the inferior laryngeal nerves to prevent fatal laryngeal paralysis) does not have any material effect on an animal during rest. Its range of activity is, however, materially reduced, largely because of loss of the capability of the heart to increase its output.

The Afferent Fibres from the Viscera.—It will have been noticed that the autonomic nervous system, as described, is an efferent system; but, throughout the areas supplied, there are also afferent fibres which carry impulses into the central nervous system. Very few of their pathways have been accurately traced. For this purpose Langley utilised the movements of a limb or tail which occurred on applying tension to organ. McDowall has shown that these reactions are very readily seen in a decapitate animal. He has also shown that in the chloralosed cat appropriate stimulation of viscera may cause dilatation of the pupil and, from the effects of nerve section, the pathways may be traced. It should perhaps be stated the afferent paths are by the posterior roots of all the spinal nerves which receive grey rami from all the sympathetic ganglia. Of special interest are the afferent fibres from the heart which have now been shown to pass in by the posterior roots of the upper thoracic and lower cervical region. This subject is discussed later in relation to sensation.

The Action of Drugs on the Autonomic Nervous System.—These are important from the physiological point of view, since it is largely by the use of drugs that the activities of the autonomic nervous system have been elucidated. As they are dealt with later they need only be mentioned here.

Sympathetic: *stimulant*—adrenaline. *Paralysant*—ergotoxine and ergotamine. **Parasympathetic:** *stimulant*—pilocarpine, choline, and acetyl-choline. *Paralysant*—atropine.

In the section on the humoral transmission of the nerve impulse we have seen that the transmission of impulses to organs or to other nerve-cells is mediated by the action of the chemical substances acetyl-choline and the adrenaline-like substance sympathin.

Nicotine, as we have seen, paralyses both systems by acting on the synapses in ganglia. The other drugs act in the region of the nerve-endings. The evidence that they do not necessarily act directly on nerve-endings is that they still continue to act after the nerve has been cut and become degenerated; indeed, the organ may be more sensitive than before. This occurs in the case of the pupil, which becomes more sensitive to adrenaline after the sympathetic supply has been cut. A suggested explanation is that there may be, between the actual nerve-ending and the organ, an increase of a receptive substance on which the drugs act.

The details of the action of the drugs are to be inferred from what has been said in relation to the general function of the autonomic nervous system, and are dealt with further in relation to the special systems of organs concerned.

The action of the autonomic nervous system may be simulated by the injection of drugs, notably of adrenaline, which acts like the sympathetic, and acetyl-choline, which acts like the parasympathetic. They are shown in the following table, also the action of ergotoxine and atropine which paralyse both respectively.

	Adrenaline.	Choline.	Ergotoxine.	Atropine.	Notes.
Pupil	O	X	X	O	Adrenaline does not dilate the pupil if applied locally.
Bronchi	O	X	X	O	Adrenaline and less so atropine are used for this purpose.
Heart rate	+	-	-	+	Atropine in small doses, less than 1/100 gr., has a reverse central effect.
Vessels, coronary.	O	X	X	O	...
„ muscle	O	O	X	O	Large doses of adrenaline will constrict all vessels.
„ skin	X	O	X	O	Ergotoxine has a special direct action.
„ intestine	X	O	X	O	Adrenaline must be applied locally.
Blood-pressure	±	-	+	±	The action result is dependent on the state of the skin vessels and the dose.
Intestinal movements except sphincters	-	+	+	-	Atropine used to alleviate spasm.
Intestinal secretion	-	+	.	-	...
Salivary secretion	+	+	..	-	The adrenaline secretion occurs after large dose. Atropine much used for this purpose.
Skin secretion	-	...
Lachrymal secretion	+	.	.	-	...
Urinary bladder	-	X	X	-	...
Uterus	*X	.	X

NOTES.—O = Dilatation. X = Constriction. . = No effects, or not investigated, or uncertain.

* Variable according to the animal. Relaxed in cats, guinea-pigs, and rats.

Drugs acting like adrenaline—Ephedrine, which prevents the destruction of adrenaline, tyramine, and a number of new drugs.

Drugs acting like acetyl-choline—Choline, pilocarpine, arecoline, also eserine, and prostigmin which prevent the destruction of acetyl-choline.

Most of these drugs have been extensively used in the study of the autonomic action, and many—especially eserine, atropine, and ephedrine, the action of which is prolonged—are used clinically.

REFERENCES.—Gaskell, Langley, Kuntz, Dale, Rosenblueth and Cannon.

CHAPTER X

THE CIRCULATORY SYSTEM

THE circulatory system consists of the *heart*, the *arteries*, or vessels which carry the blood from the heart to other parts of the body, the *veins*, or vessels which carry the blood back to the heart again, and the *capillaries*, a network of minute tubes which connect the terminations of the smallest arteries to the commencements of the smallest veins.

The Heart.

The heart is the great muscular pump of the circulatory system. It lies in the chest between the right and left lungs, and is enclosed in a bag called the *pericardium*, the function of which is discussed later.

The Chambers of the Heart.—The interior of the heart is divided by a longitudinal partition into two muscular cavities, the right and left. Each of these chambers is again subdivided transversely into an upper and a lower portion, called respectively, auricle and ventricle, which freely communicate one with the other; the aperture of communication, however, is guarded by valves, so disposed as to allow blood to pass freely from the auricle into the ventricle, but not in the opposite direction. There are thus four cavities in the heart—the auricle and ventricle of one side being quite separate from those of the other (figs. 40 and 41).

At this stage the student should examine in detail the structure of the heart of a mammal. If a human heart is not conveniently available the heart of a sheep or rabbit, which in all but size is almost identical, should be studied. It is best in each instance to commence by identifying the thick aorta which arises from the thickest chamber of the heart—the left ventricle—and to trace the course of the blood backwards.

The chambers of the heart are lined continuously by a thin membrane, the *endocardium*, which is continuous with the endothelial lining of the blood-vessels.

The **right auricle** is a thin-walled cavity, prolonged at one corner into a tongue-shaped portion, the right auricular appendix. Into it open the superior and inferior venæ cavæ, or great veins, which convey the blood from all parts of the body to the heart. The

opening of the inferior vena cava is protected and partly covered by a membrane called the *Eustachian valve*. In the posterior wall of the auricle is a slight depression called the *fossa ovalis*, where in the foetus there was an opening between the auricles which permitted the blood to pass to the left side of the heart without passing through the lungs.

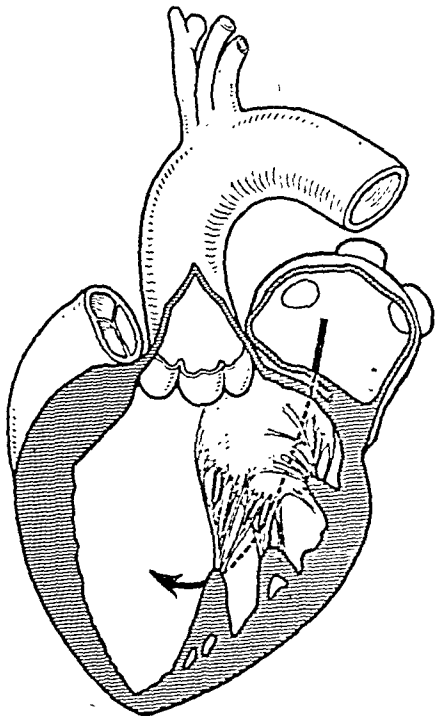


FIG. 40.—The interior of the heart showing the different character of the aortic and mitral valves (see text). To the latter are seen attached the chordæ tendineæ, the papillary muscles.

The **right ventricle** occupies the chief part of the anterior surface of the heart. It takes no part in the formation of the apex. Blood enters it from the right auricle by the *tricuspid valve* and leaves it by the *pulmonary artery* which is guarded by the *pulmonary valve*.

The **left auricle** receives the blood from the lungs by four *pulmonary veins* and passes it on through the *mitral valve* to the left ventricle.

The **left ventricle** has a wall which in man is about three times as thick as that of the right ventricle since it has to pump the blood through the body generally. The blood leaves by the *aorta* which is guarded by the *aortic valve*.

Valves.—The arrangement of the heart's valves is such that the

blood can pass only in one direction.

The *tricuspid* valve presents *three* principal cusps or subdivisions and the mitral or *bicuspid* valve has *two* such portions. Each cusp is of triangular form. Its base is continuous with the bases of the neighbouring portions, and with them forms an annular membrane round the auriculo-ventricular opening, and is fixed to the tendinous ring which encircles the orifice.

While the bases of the cusps of the valves are fixed to the tendinous rings, their borders are fastened by slender tendinous fibres, the *chordæ tendineæ*, to the papillary muscles which project from the internal surface of the walls of the ventricles (see fig. 40).

The preceding description applies equally to both the mitral and the tricuspid valve; but it should be added that the mitral is

considerably thicker and stronger than the tricuspid, in accordance with the greater force which it is called upon to resist.

The *semilunar valves* guard the orifices of the pulmonary artery and of the aorta. They are nearly alike on the two sides of the heart; but the aortic valves are more strongly constructed than the pulmonary valves, in accordance with the greater pressure which they have to withstand. Each valve consists of three parts which are of semilunar shape, the convex margin of each being attached to a fibrous ring at the place of junction of the artery to the ventricle, and the concave or nearly straight border being free, so as to form a little pouch like a watch-pocket (fig. 40). In the centre of the free edge of the pouch, which contains a fine cord of fibrous tissue, is a small fibrous nodule, the *corpus Arantii*, and from this and from the attached border fine fibres extend into every part of the mid-substance of the valve, except a small lunated area just within the free edge, on each side of the corpus Arantii. Here the valve is thinnest, and composed of little more than the endocardium. Thus constructed and attached, the three semilunar pouches are placed side by side round the arterial orifice of each ventricle; they are separated by the blood passing out of the ventricle, but immediately afterwards are pressed together so as to prevent any return. Opposite each of the semilunar cusps, both in the aorta and pulmonary artery, there is a bulging outwards of the wall of the vessel: these bulgings are called the *sinuses of Valsalva*. From two of these sinuses just behind the aortic cusps open the coronary arteries which supply blood to the heart during its relaxed phase.

Course of the Circulation.

The blood is conveyed away from the left ventricle (as in the diagram, fig. 41) and has the following courses, heart → arteries, → arterioles, → capillaries, → venules → veins → heart.

From the right auricle the blood passes to the right ventricle, then by the pulmonary artery, which divides into two, one for each lung, then through the pulmonary capillaries, and through the pulmonary veins (two from each lung) to the left auricle. From here it passes into the left ventricle, which brings us back to our starting place.

The complete circulation is thus made up of two circuits, the one, a shorter circuit from the right side of the heart to the lungs and back again to the left side of the heart; the other and longer circuit, from the left side of the heart to all parts of the body and back again to the right side. The circulations through the lungs and through the system generally are respectively named the **Pulmonary** and **Systemic** or *lesser* and *greater* circulations. It will be noticed

also in the same figure that a portion of the stream of blood having been diverted once into the capillaries of the intestinal canal, and some other abdominal organs, and gathered up again into a single stream, is a second time divided in its passage through the liver, before it finally reaches the heart and completes a revolution. This subordinate stream through the liver is called the **Portal** circulation. A somewhat similar accessory circulation is that through the kidneys, called the **Renal** circulation. The difference of colours in fig. 41 indicates roughly the difference between *arterial* and *venous* blood

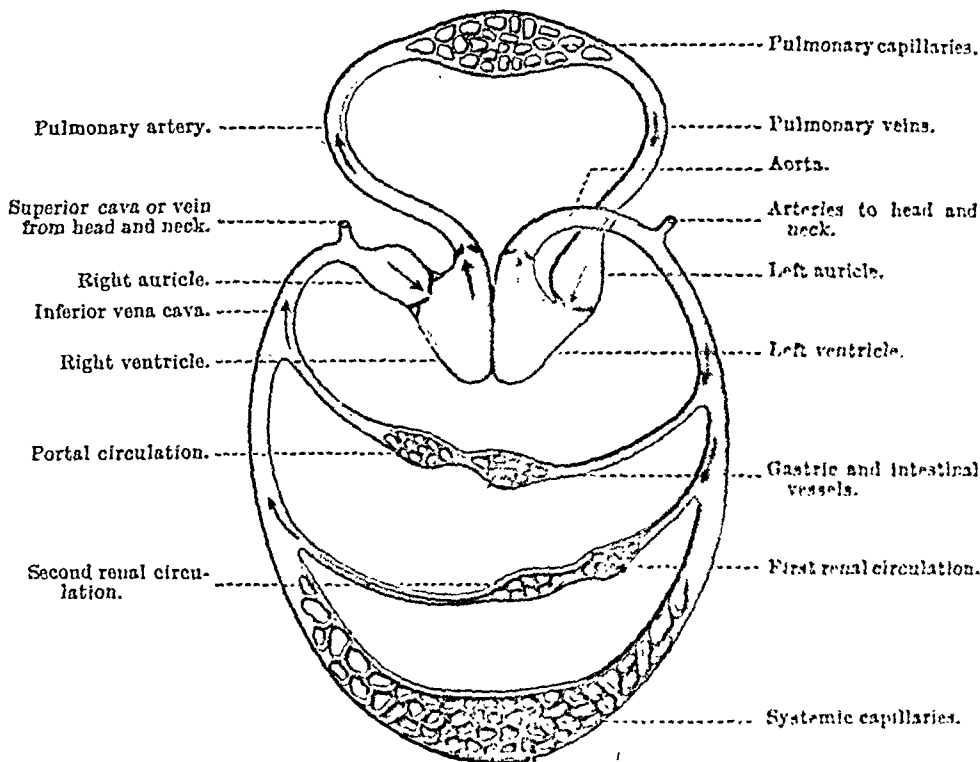


FIG. 41.—Diagram of the circulation.

The blood is oxygenated in the lungs, and the formation of oxy-hæmoglobin gives to the blood a bright red colour. This oxygenated or arterial blood (contained in the pulmonary veins, the left side of the heart, and systemic arteries) is in part reduced in the tissues, and the deoxygenated hæmoglobin is darker in tint than the oxy-hæmoglobin; this venous blood passes by the systemic veins to the right side of the heart and thence by the pulmonary artery to the lungs, where it once more receives a fresh supply of oxygen.

It should, however, be noted that the lungs, like the rest of the body, are also supplied with arterial blood, which reaches them by the bronchial arteries.

The Structure of the Vessels in Relation to their Function.

The vascular system is lined throughout by a layer of elongated pavement cells known as endothelium. The cells of this layer contain relatively large quantities of lipid material which probably has important physiological functions. Friction is reduced to a minimum and the blood corpuscles slip easily along its surface. If it is broken it heals rapidly; at the broken point a blood clot commonly occurs. As we shall see, the capillaries are composed of endothelium only, with a few scattered cells on the outside, but the larger vessels have several coats according to their needs. Muscle of the unstripped variety is added to give contractility so that the vessel may change its calibre. Elastic tissue gives additional elasticity, while strands of fibrous tissue confer strength to the whole and makes vessels capable of withstanding pressures of over 300 millimetres of mercury in certain circumstances.

Arteries of various sizes vary in their structure. The muscular coats are best seen in those smaller vessels which change their calibre, while elastic tissue preponderates in the large arteries where, as we shall see, it is so important for the maintenance of the blood-pressure while the heart is filling. A thin layer of elastic tissue usually supports the endothelial lining. Arterioles are especially muscular.

The veins, in which the blood-pressure is much lower, have much thinner walls than the corresponding arteries. On the whole they contain less elastic and muscular tissue but often relatively more fibrous tissue. The veins near the heart have well-marked circular muscle, while in those in the bones and central nervous system there is none. Venules are more muscular than veins.

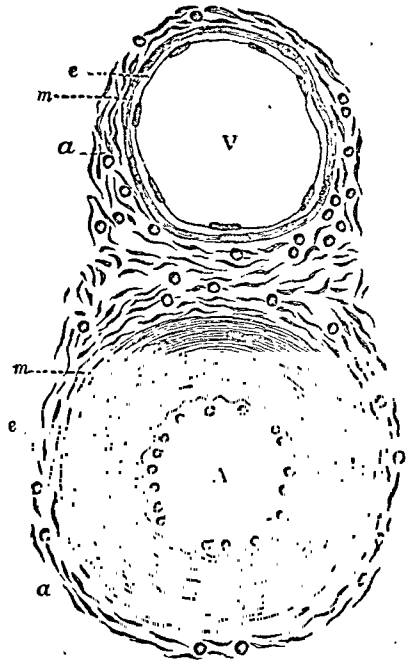


FIG. 42.—Transverse section through a small artery and vein of the mucous membrane of a child's epiglottis; the artery is thick-walled and the vein thin-walled. A. Artery, the letter is placed in the lumen of the vessel. e, Endothelial cells with nuclei clearly visible; these cells appear very thick from the contracted state of the vessel. Outside them a double wavy line marks the elastic layer of the tunica intima. m. Tunica media, consisting of unstripped muscle fibres circularly arranged; their nuclei are well seen. a, Part of the tunica adventitia showing bundles of connective-tissue fibre in section, with the circular nuclei of the connective-tissue corpuscles. This coat gradually merges into the surrounding connective tissue. v. In the lumen of the vein. The other letters are used as in the artery. The muscular coat of the vein (m) is seen to be much thinner than that of the artery. $\times 850$. (Klein and Noble Smith.)

Because of this histological structure the arteries are much more rigid than the veins and do not collapse when empty. It was because of this that the ancients thought they contained air and called them arteries. At death they go into spasm and empty themselves.

Nerves.—Most of the arteries are surrounded by a plexus of nerves, which terminate in a network between the muscle-fibres. A vein may be punctured almost painlessly, and this is commonly done when drawing off blood from the median basilic superficial vein of the forearm. The puncturing of an artery causes exquisite pain.

Valves.—One main distinction between arteries and veins is the presence of valves in the latter vessels. The general construction of these valves is similar to that of the semilunar valves of the aorta and pulmonary artery, already described; but their free margins are



FIG. 43.—Diagram showing part of a vein laid open and spread out, with two pairs of valves.

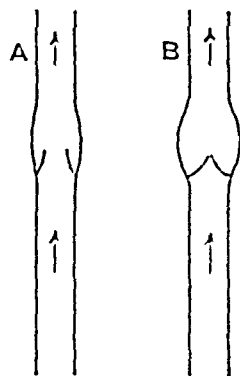


FIG. 44. — A, Vein with valves open. B, with valves closed; with ballooning of the vein above.

turned in the opposite direction, *i.e.* towards the heart, so as to prevent any movement of blood backward. They are commonly placed in pairs, at various distances in different veins, but almost uniformly in each (fig. 43). In the smaller veins single valves are often met with; and three or four are sometimes placed together, or near one another, in the largest veins, such as the subclavian, at their junction with the jugular veins. They are composed of an outgrowth of the subendothelial tissue covered with endothelium. Their situation in the superficial veins of the forearm is readily discovered by pressing along their surface, in the direction opposite to the venous current, *i.e.* from the elbow towards the wrist; little swellings appear in the position of each pair of valves. These swellings at once disappear when the pressure is removed.

Valves are not equally numerous in all veins, and in many they are absent altogether. They are most numerous in the veins of the extremities, and more so in those of the leg than the arm. They are commonly *absent* in the most minute veins and venules, and, as a

general rule, there are few or none in those which are not subject to muscular pressure. This fact is of considerable physiological importance, since the compression of the veins by the muscles is an important factor in assisting the return of blood to the heart.

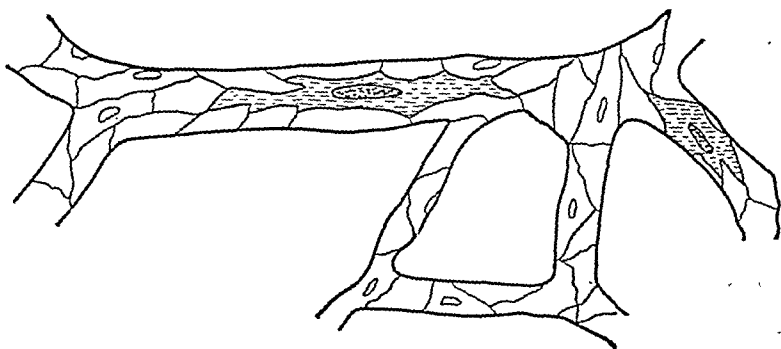


FIG. 45.—Diagram of capillary showing the nucleated endothelium of which it is composed and two Rouget cells. (After Klein, Noble Smith, and Vimtrup.)

The Capillaries.—In most cases the blood finds its way from the small arteries to the small veins through a network of minute vessels, the capillaries. But in certain cases (parathyroid, spleen, the thyroid of some animals, erectile tissue, the placenta, and the embryonic liver and kidney) the connecting systems of vessels

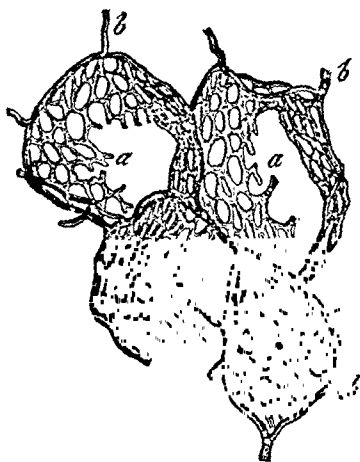


FIG. 46.—Network of capillary vessels of the air-cells of the horse's lung magnified. *a, a*, Capillaries proceeding from *b*, terminal branches of the pulmonary artery. (Frey.)

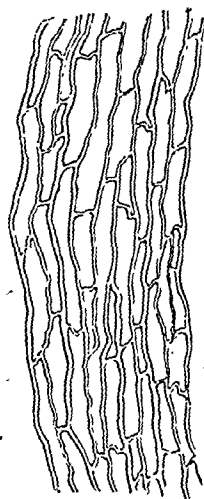


FIG. 47.—Injected capillary vessels of muscle seen with a low magnifying power. (Sharpey.)

are larger and have an irregular shape; these vessels are termed *sinusoids*.

The walls of both capillaries and sinusoids are composed of

endothelium—a single layer of elongated flattened and nucleated cells, so joined and dovetailed together as to form a continuous transparent membrane (fig. 45).

The Nature of Capillary Contraction and Dilatation.—There has been considerable discussion regarding the exact change which takes place in the wall of a capillary when it contracts. The evidence is now complete as a result of cinematographic evidence that the cells of the capillary wall have the power of changing their shape. When the cells swell they can obliterate the lumen of the capillary. This really was the original view of Stricker in 1876 on the basis of direct observation, but subsequently it was considered that the scattered cells sometimes seen on the capillaries, and known as Rouget cells, were responsible. These cells have now been shown to be macrophages. The capillaries have been seen to contract before these special cells are developed.

How chemical substances cause the cells to swell is, however, unknown. It seems most probable that some change takes place in the cell wall and water is imbibed, while a reversal of this process would re-establish the lumen.

The *diameter* of the capillary vessels varies slightly in the different tissues of the body, the most common size being about $\frac{1}{2000}$ th of an inch (12μ).

The form of the capillary network and the size of the individual capillaries vary considerably in different parts of the body.

It may be held as a general rule that the greater the activities of an organ are, the more vascular it is. Hence the narrowness of the interspaces in all glandular organs, in mucous membranes, and in growing parts, and their much greater width in bones, ligaments, and other comparatively inactive tissues.

Arterio-Venous Anastomoses.—In some regions the arterioles and venules communicate directly, for example in the ear of the rabbit. The function of these anastomoses appears to be to allow hot blood to pass freely through the part for purposes of cooling (Grant). (See fig. 74.)

Collateral Circulation.

When the main artery or vein of a part of the body is occluded, collateral circulations rapidly open up and quite small vessels may enlarge and take over the function of the larger vessels. This is possible because of the free anastomosis of arteries and of veins, but the exact stimulus which determines the enlargement is not known. In the case of the arm, for example, if the brachial artery is blocked the circumflex artery may enlarge and become the main supply of the arm.

CHAPTER XI

THE CIRCULATION

PREVIOUS to the time of Harvey (1628), the vaguest notions prevailed regarding the use and movements of the blood. The arteries were supposed by some to contain air, because when an animal is killed, they are usually found to be empty, their spasm at death having driven the blood into the veins. It was imagined that the air got into the arteries from the lungs and supplied vital spirit to the body. The brain, on the other hand, supplied animal spirit.

There was an idea that the blood was subject to a to-and-fro movement which was confined to the veins. The proofs that the movement is in a circle were discovered by William Harvey, to whom also belongs the credit of pointing out the methods by which almost every physiological problem must be studied. In the first place there must be correct anatomical knowledge, and in the second there must be experiment, by which deductions from structure can be tested; this second method is the more important of the two. Harvey's work on the circulation fulfilled both these requirements.

Harvey studied at Cambridge and Padua but became physician to King Charles I, and to St Bartholomew's Hospital, London.

The structural or anatomical facts on which he relied were:—

A. The existence of two distinct sets of tubes in connection with the heart: the arteries and the veins.

B. The existence in the heart, and also in the veins, of valves which allow the passage of the blood in one direction only.

His experimental findings were:—

1. That the blood spurts with great force and in a jerky manner from an artery opened during life, each jerk corresponding with a beat of the heart.

2. That if the large veins near the heart are tied, the heart becomes pale, flaccid, and bloodless, and on removal of the ligature blood again flows into the heart.

3. If the aorta is tied, the heart becomes distended with blood, and cannot empty itself until the ligature is removed.

4. The preceding experiments were performed on animals, but by the following experiment he showed that the circulation is a fact in man also; if a ligature is drawn tightly round a limb to compress the artery to the part no blood can enter it, and it becomes pale and cold. If the ligature is relaxed so that only the veins are

compressed blood can enter but cannot leave and the limb becomes swollen. If the ligature is removed, the limb soon regains its normal appearance.

5. Harvey also measured the amount of blood which the heart could hold and the total amount in the body. He reasoned that in order to make it possible for the heart to pump out such an amount at each beat the same blood must be used over and over again.

6. If an artery is wounded, hæmorrhage may be stopped by pressure applied between the heart and the wound; but if the wound is in a vein, the pressure must be applied beyond the seat of injury.

Since Harvey's time many other proofs have accumulated. For instance:—

Perhaps the most satisfactory proof of the circulation is one now within the reach of every student, though beyond that of Harvey. It consists in actually seeing the passage of the blood from small arteries through capillaries into veins in the transparent parts of animals, such as the tail of a tadpole or the web of a frog's foot. Harvey could not follow this part of the circulation, for he had no lenses sufficiently powerful to enable him to see it. Harvey's idea of the circulation here was that the arteries carried the blood to the tissues, which he considered to be of the nature of a sponge, and the veins collected the blood again, much in the same way as drainage pipes would collect the water of a swamp. The discovery that the ends of the arteries are connected to the beginnings of veins by a definite system of small tubes we now call capillaries was made by Malpighi, in the year 1661. He first observed them in the lung of the frog, and Leeuwenhoek, seven years later, saw the circulation in the tail of a tadpole.

The student is referred to a small book on the subject by Singer, which gives a convenient summary of the ancient views.

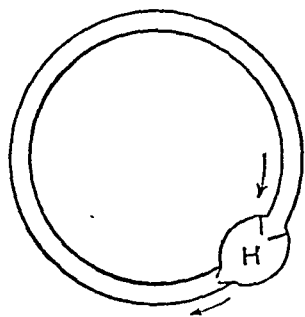


FIG. 48.—Simple model of the circulation.

The Principle of the Circulation.—

The simplest possible way in which we can represent the circulatory system is shown in fig. 48. Suppose we had a ring of tubing with a bulb (H) which could be compressed by hand. If the apparatus were filled with fluid and the bulb compressed there would be a to-and-fro movement of the fluid. The presence of valves, however, which permit the flow in one direction only would convert the flow into a circulation as illustrated in

the figure. If the contraction and relaxation of the bulb which corresponds to the heart were repeated often enough the fluid would move round and round within the tubular ring.

The main factor in the circulation is difference of pressure. In general terms fluid flows from points of high pressure to those of lower pressure. This difference of pressure is produced in the first instance by the contraction of the heart, but we shall find in our study of the vessels that some of this pressure is stored up in the elastic arterial walls, the recoil of which keeps up the circulation during the periods when the heart is resting.

In worms the circulatory system is almost as simple as in the model just described; the heart is a long contractile tube provided

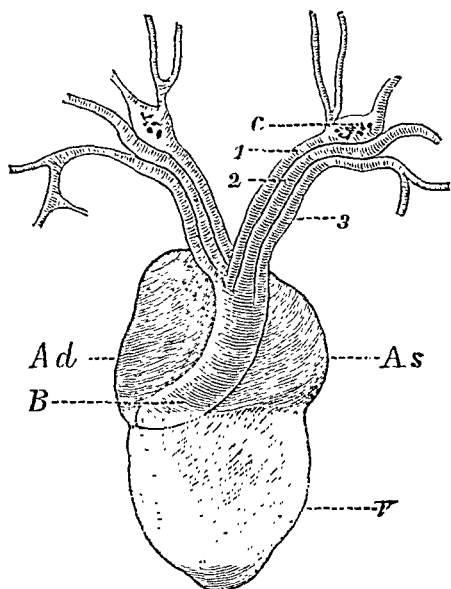


FIG. 49.—The heart of a frog (*Rana esculenta*) from the front. V, ventricle; Ad, right auricle; As, left auricle; B, bulbus arteriosus, dividing into right and left aortæ. (Ecker.)

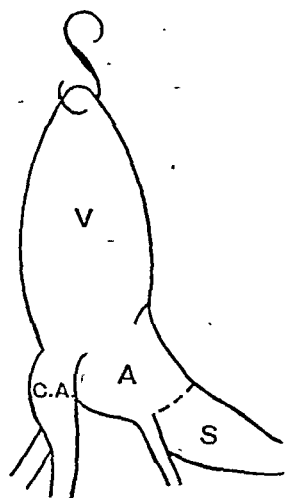


FIG. 50.—Diagram of frog heart. V = ventricle, A = auricle, S = sinus, C.A. = bulbus arteriosus from which the aorta originates. Between the sinus and the auricle the sino-auricular junction is indicated by the dotted line.

with valves; along it a wave of contraction passes and presses the blood forwards into the aorta at its ventral end; this divides into arteries for the supply of the body; the blood passes through these to capillaries, and is collected by veins which converge to one or two main trunks that enter the heart at its dorsal end.

In fishes the heart is divided into a number of chambers placed in single file, one in front of the other.

Taking the frog as an instance of an amphibian, we find the heart more complex, and the simple action of the heart muscle, as we have described it in the hearts of worm and fish, is correspondingly modified. There is only one ventricle, but there are two auricles, right and left.

The ventricle contains mixed blood, since it receives arterial

blood from the left auricle (which is the smaller of the two), and venous blood from the right auricle; the right auricle receives the venous blood from the sinus, which in turn receives it from the systemic veins. The left auricle, as in man, receives the blood from the pulmonary veins.

When the ventricle contracts, it forces the blood onward into the aortic bulb which divides into branches on each side for the supply of the head (fig. 49, 1), lungs and skin (fig. 49, 3), and the third branch (fig. 49, 2), unites with its fellow of the opposite side to form the thoracic aorta for the supply of the rest of the body.

In reptiles the division of the ventricle into two is beginning, but it is not complete till we reach the birds. The heart reaches its fullest development in mammals, and we have already described the human as an example of the mammalian heart. The sinus is not present as a distinct chamber in the mammalian heart (except in a very early foetal stage), but is represented by that portion of the right auricle at which the large veins enter.

CHAPTER XII

PHYSIOLOGY OF THE HEART

The Cardiac Cycle

THE series of changes which occurs in the heart constitutes the *cardiac cycle*. This must be distinguished from the course of the circulation. The term "cycle" indicates that if one observes the heart at any particular moment, the heart from that moment onwards undergoes certain changes until it once more assumes the same condition that it had at the moment when the observation commenced, when the cycle is again repeated, and so on. This series of changes consists of alternate contraction and relaxation. Contraction is known as **systole**, and relaxation as **diastole**.

The contraction of the two auricles takes place simultaneously, and constitutes the *auricular systole*; this is followed by the simultaneous contraction of the two ventricles, *ventricular systole*; after each systole the auricles and ventricles relax or go into diastole in the same order. The auricular diastole begins before ventricular systole is over and is followed by ventricular diastole. The cycle again commences with the auricular systole.

Taking 72 as an average number of heart-beats per minute, each cycle will occupy $\frac{1}{72}$ of a minute, or a little more than 0.8 of a second. This may be approximately distributed in the following way:—

Auricular systole	about 0.05	+ Auricular diastole	0.75	= 0.8
Ventricular systole	0.3	+ Ventricular diastole	0.5	= 0.8

If the speed of the heart is quickened, the time occupied by each cycle is diminished, but the diminution affects chiefly the diastole. These different parts of the cycle must next be studied in detail.

Auricular Diastole.—During this time, the blood from the large veins is flowing into the auricles, the pressure in the veins though very low being greater than that in the empty auricles. The blood expands the auricles. As soon, however, as the auriculo-ventricular valves open the blood passes through into the ventricles. These valves open as soon as the pressure in the auricles becomes

greater than that in the ventricles, that is at the beginning of ventricular diastole.

Auricular Systole.—By contracting, the auricles empty themselves into the ventricles which are already full. The contraction commences at the entrance of the great veins, and is thence propagated towards the auriculo-ventricular opening. Regurgitation into the veins is prevented, not by valves, but by the contraction of the muscle around the venous inlets.

Ventricular Diastole.—During the last part of the auricular diastole and the whole of the auricular systole, the ventricles are relaxed and then filled with blood. The dilatation of the ventricles is brought about in virtue of their elasticity and by the pressure of the venous blood.

Ventricular Systole.—This is the contraction of the ventricles, and it occupies more time than the auricular systole; when it occurs the auriculo-ventricular valves are closed and prevent regurgitation into the auricles, and when the force of the systole is great enough, the pressure within the ventricles exceeds that in the large arteries which originate from them; the semilunar valves are opened, and the ventricles empty themselves, the left into the aorta, the right into the pulmonary artery.

Action of the Valves and Filling of the Heart.

1. The ventricles are filled by the pressure of the blood in the veins and the fluid ejected from the auricles during their systole causes slight additional distension of the ventricles.

The auricles are therefore to be looked upon as accessory to ventricular filling, but not essential. In cardiac disease, *e.g.* auricular fibrillation, the auricles cease to act normally and ventricular filling depends solely on venous pressure. It is important to observe that the main filling of the ventricles takes place in the first third of diastole. See volume curves of heart, fig. 52. The *auriculo-ventricular valves* are gradually brought into place by eddies and by blood getting behind the cusps and lifting them up; by the time diastole is complete, the valves are in apposition, and are firmly closed by the pressure set up by the systole of the ventricles. The margins of the cusps of the valves are still more secured in apposition to one another by the simultaneous contraction of the *musculi papillares*, whose *chordæ tendinæ* have a special mode of attachment for this object. The cusps of the auriculo-ventricular valves meet not by their edges only, but also by the opposed surfaces of their thin free borders.

The contraction of the papillary muscles to the tip of which are attached the chordæ tendineæ prevents the auriculo-ventricular valves being pressed back into the auricles when the ventricles contract.

2. *The Semilunar Valves.*—The first result of the contraction of the ventricles is the closure of the auriculo-ventricular valves, and as soon as this has been effected the intraventricular pressure begins to rise. It quickly reaches a point at which it equals the aortic pressure, and then exceeds it, and as soon as this pressure difference has been established the aortic valves are opened and blood flows from the ventricle into the aorta. The valves are kept open as long as the intraventricular pressure exceeds the aortic. As soon as the heart has emptied itself, the ventricle begins to relax. The valves tend to fall into position because of eddies set up by the outrushing blood, and, as soon as the pressure in the ventricles falls below the pressure in the aorta they are closed sharply.

Time Relations of the Events of the Cardiac Cycle.

These have been studied by investigating the changes in pressure inside the heart (**endocardiac pressure**) and the changes in the volume of the organ. A tube or sound is passed into the part of the heart concerned. For the right side of the heart it may be passed down the jugular vein.

Records may be taken by connecting the sound to a manometer on the principle of Marey's tambour but of stouter material. The Hürthle or Gadd manometer has a moving membrane of thick rubber or metal respectively so that it responds rapidly. In each instance the recording apparatus is connected to the sound by tubing filled with anticoagulant fluid as in recording blood-pressure.

By far the most accurate results, however, are obtained by connecting the cardiac cavity by means of a tube with an optical recorder instead of a tambour bearing a lever. Recorders for the purpose were introduced by Frank, elaborated by Piper and more recently by Wiggers, Professor of Physiology in Western Reserve University, U.S.A. In this apparatus a small rubber membrane is stretched over the end of a tube with a flattened side. On the membrane next the flattened side is attached a mirror from which a beam of light is reflected (fig. 51). The movements of the beam are recorded on a moving photographic film, as in the electrocardiograph. The apparatus is standardised by attaching it to an ordinary U-tube mercury manometer and noting the extent of the movement of the beam when the pressure in the system is changed a known amount. A record taken by an optical recorder is shown in fig. 52, and from such observations the following phases

of the cardiac cycle have been determined by Piper and by Wiggers. The actual times need not be committed to memory, but the causes of each change of pressure should be noted.

(1) Auricular systole 0.05 sec., diastole 0.75.

(2) Ventricular systole. Total duration 0.33 to 0.23 sec. according to the rate of the heart (I-III in fig. 52). The period between II and III is known as *systolic plateau*.

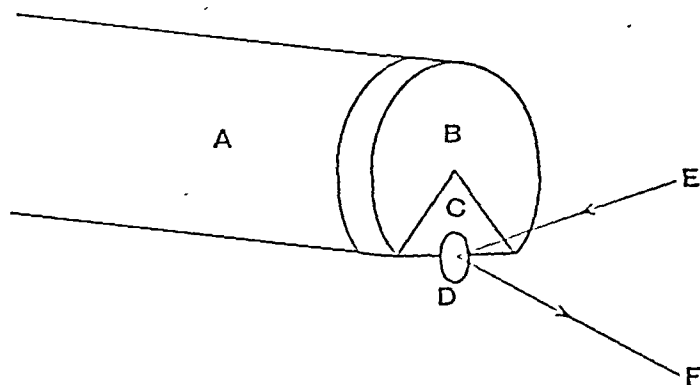


FIG. 51.—Modified Wiggers manometer.—A, glass tube with flattened side; B, rubber membrane stretched over end of A; C, celluloid triangle cemented on to B; D, small mirror; E and F, incident and reflected rays respectively.

During the first part of the systole the ventricle is a closed cavity and for this period Wiggers uses the term *Isometric Phase*.* In the second part blood is expelled into the aorta (*Ejection Phase*).

(3) Ventricular diastole. There are two distinct phases of ventricular diastole (III-I). In the first the ventricle does not fill and in the second it does.

(a) Early diastole (III-IV), from the beginning of relaxation till closure of aortic valves and during isometric relaxation in which the ventricle is again a closed cavity, *i.e.* before the auriculo-ventricular valves open.

(b) The remainder and most important part of diastole is divided into two phases (IV-V and V-VI) during which the inflow is rapid and slow respectively. At the end of the slow phase (V-VI) the contraction of the auricle occurs which hastens the last part of diastolic filling of the ventricle.

The total length of diastole varies very much according to the rate of the heart. The important point, however, must be noted that the main filling of the heart occurs during the first third (IV-V) of diastole and that consequently a shortening of diastole

* So called because the ventricular muscle develops tension but has not shortened.

which may occur between v and vi does not materially affect the total filling.

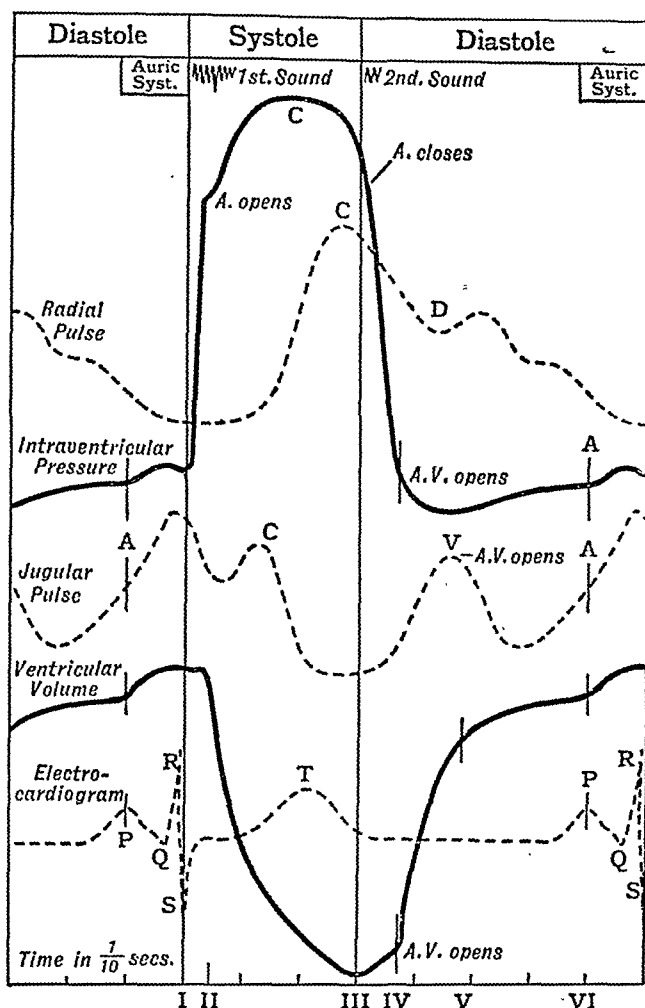


FIG. 52.—Diagram showing simultaneous ventricular pressure and volume records (modified from Wiggers). I-II, period of isometric contraction; II-III, period of ejection; III-IV, early diastole; IV-V, period of rapid inflow; V-VI, period of slow inflow. The volume record has been taken by means of a cardiometer (see fig. 60) attached to an optical recorder. Some similar records such as those taken by Piper show a small change between III and IV which corresponds to the closure of the aortic valves. The dotted lines indicate the radial and jugular pulses and the electro-cardiogram.

Intra-Auricular Pressure.

The chief interest in this pressure lies in the fact that the changes which occur in the auricle are similar to those which appear in a record of a venous pulse (p. 141) except that in the auricular record the waves occur earlier in the cardiac cycle. The changes which take place are discussed in relation to the venous pulse.

The actual pressure in the auricles is not normally in excess of 5 mm. Hg. This indicates the enormous effect which a leaky

mitral valve must have, since the systolic pressure in the left ventricle varies commonly from about 120 mm. during rest to about 200 mm. Hg during exercise. The systolic pressure in the right ventricle is about a quarter of that in the left.

The Sounds of the Heart.

When the ear is placed over the region of the heart, two *sounds* which follow in quick succession, and are succeeded by a *pause* or period of silence, may be heard at every beat of the heart. The *first* or *systolic* sound is dull and prolonged; its commencement coincides with the impact of the heart against the chest wall, and it lasts during the greater part of the ventricular systole; it just precedes the pulse at the wrist. The *second* or *diastolic* sound is shorter and sharper, with a somewhat flapping character; it follows the end of ventricular systole, and is audible just after the radial pulse is felt. The sounds are often compared to the syllables, *lubb—dūp*.

Causes.—*First Sound*—Two factors enter into the production of this sound: the muscular contraction of the heart, and the closure of the auriculo-ventricular valves. The following facts are evidence that the muscular contractions are concerned: (1) the sound resembles that produced by a contracting voluntary muscle; (2) the sound may be heard when the heart is empty, as in the excised heart. With regard to (1): although the cardiac contraction is a twitch and that of voluntary muscle normally a tetanus, it must be borne in mind that unequal tension repeatedly set up in the intricately interlaced fibres of the ventricular wall would lead to the production of a sound. It is important, however, to realise that even the valvular element in the sound depends on the muscular contraction, since the latter is indirectly responsible for the closure of the valves. The loudness of the first sound is therefore to some extent an indication of the fitness of the heart-muscle and its enfeeblement may indicate approaching heart failure, *e.g.* in fever.

The cause of the *second sound* is simpler and consists entirely of the vibration consequent on the sudden stretching of the semilunar valves when they are pressed down across the orifices of the aorta and pulmonary artery. The influence of these valves in producing the sound was first demonstrated by Hope, who experimented with the hearts of calves. In these experiments two delicate curved needles were inserted, one into the aorta, and another into the pulmonary artery, below the line of attachment of the semilunar valves, and, after being carried upwards about half an inch, were brought out again through the coats of the respective vessels, so that in each vessel one valve was included between the arterial walls and the wire. Upon applying the stethoscope to the vessels

after such an operation, the second sound ceased to be audible. Disease of these valves, when sufficient to interfere with their efficient action, also demonstrates the same fact by modifying the second sound or destroying its distinctness. The *dr̄p* becomes *duff*.

The loudness of the second sound depends on the height of the arterial pressure, but like that of the first sound it may be masked by a thick chest wall.

The contraction of the auricles is inaudible.

The first sound is heard most distinctly at the apex-beat in the fifth interspace; the second sound is best heard over the second *right* costal cartilage—that is, the place where the aorta lies nearest to the surface. The pulmonary and aortic valves generally close simultaneously. In some cases, however, the aortic may close slightly before the pulmonary valves, giving rise to a “reduplicated second sound.” The pulmonary contribution to this sound is best heard over the second *left* costal cartilage.

The **apex-beat** in man is felt normally in the fifth left intercostal space three and a half inches from the middle line. It is caused by two factors. The heart becomes hard and tense and is therefore capable of causing an impulse against the chest-wall. Its attachment to the aorta becomes more rigid, and when the aortic pressure suddenly rises during systole the aorta, tending to straighten out, causes the heart to press more firmly against the thoracic wall; the aorta cannot straighten to any extent in a backward direction because of the rigid vertebral column behind it.

When the left ventricle is enlarged the apex-beat may be displaced appreciably downwards and to the left.

Cardiographs.

A cardiograph is an instrument for obtaining a graphic record of the heart's movements. In animals the heart may be exposed,

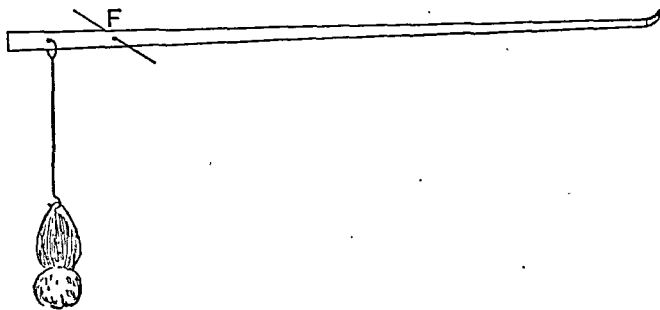


FIG. 53.—Simple cardiograph for frog's heart.

and levers connected to its various parts may be employed to write on a revolving blackened surface.

A simple instrument for the frog's heart is shown in fig. 53.

The sternum of the pithed frog having been removed, the pericardium opened, and the frænum (a small band from the back of the heart to the pericardium) divided, the heart is pulled through the opening, a minute hook placed in its apex, and this is fixed by a thread to a lever which records, as in the figure. The wave of contraction starts at the sinus, this is followed by the auricular systole, and later by the ventricular systole and pause. An actual record is seen later in fig. 55.

A number of cardiographs have been devised for recording the beat of the human heart at its apex. Since the information obtained from the use of such apparatus is little more than that from the pulse they have been given up.

The Cause of the Heart-Beat.

At one time the rhythm which cardiac muscle exhibits was thought to be due to the action of the nerves which supply it. We now know that the property of rhythmical contraction resides in muscular tissue itself, though during life it is normally controlled and regulated by its nerves. This is expressed by saying that cardiac rhythm is *myogenic* not *neurogenic*. A few physiologists still maintain the older neurogenic theory, but the majority of them have worked chiefly on the hearts of invertebrate animals, whose mechanism may be a different one. The striking observation made by early observers that the heart, especially an amphibian heart, will continue to beat after its removal from the body, is not proof either way as such a heart still contains many nervous structures. A mammalian heart will beat only for a few minutes outside the body unless supplied with blood or a substitute. But so far as the vertebrate heart is concerned, the myogenic theory is now held, because: (1) the foetal heart manifests rhythm long before any nerves reach it; (2) the apex of the ventricle of such animals as frogs and tortoises can be made to beat rhythmically by perfusing it with suitable fluids under pressure, and this part of the heart has few nerves and no ganglion cells; and (3) the rate of conduction of the excitation is slow, and corresponds to the rate of muscular rather than of nervous conduction.

Conduction in the Heart.

As already stated, the slow rate of propagation of the excitation-wave points to its travelling by a muscular rather than a nervous pathway, and histology supports this view, the muscle-fibres being connected to each other by intercellular bridges of protoplasm (see

p. 50). Experimental proof may be obtained in the following way: A strip of the heart-wall is taken and several cuts going nearly completely across it are made first from one side then from the other. All the nerves must be cut through at least once, so that the only tissue not severed is muscular. The strip still continues to beat. In other words, the propagation is *myodromic*. The passage of the wave from one chamber to another is also myodromic. The slow rate of propagation indicates that this is so, and the view has been fully proved by the discovery of muscular strands, passing across from one chamber to the next.

In the frog under normal conditions the wave of contraction in the heart starts at the sinus, and travels over the auricles to the ventricle; the irritability of the muscle and the power of rhythmic contractility are greatest in the sinus, less in the auricles, and still less in the ventricle. Under ordinary conditions the apical portion of the ventricle exhibits very slight power of spontaneous contraction. The importance of the sinus as the starting-point of the contraction can be shown by warming it. If a frog's heart is warmed by bathing it in warm salt solution at about body temperature, it beats faster; this is due to the sinus starting a larger number of excitatory waves in a given time; this may be demonstrated by warming localised portions of the heart by a small heated rod; if the sinus is warmed the heart beats faster, but if the auricles or ventricle are warmed there is no alteration in the heart's rate. The sinus in the frog's heart, and that portion of the right auricle in the mammal's heart which corresponds to the sinus, are always the last parts of the heart to cease beating at death, or after removal from the body (*ultima moriens*, Harvey). This is an additional proof of the superior rhythmical power which the sinus possesses, but this power is possessed by all cardiac muscle to a lesser degree.

In the frog's heart there is an obvious muscular connection between the auricles and ventricle along which the impulses pass. By an arrangement of ligatures, or, better, of clamps, one part of the heart may be isolated from the rest, and the contraction may be made to stop in the portion of the heart muscle in which it begins. It must not, however, be thought that the wave of contraction is incapable of passing over the heart in any other direction than from the sinus onwards; for it has been shown that by the application of appropriate stimuli at appropriate instants, the natural sequence of beats may be reversed, and the contraction starting at the arterial part of the ventricle may pass to the auricles and then to the sinus. If clamps or ligatures are not applied sufficiently tightly one often sees partial blocking; a few waves get through but not all; or, if the ventricular wall is left connected with other parts of the heart by only a small portion of

undivided muscular tissue, the effect is much the same: the wave is only able to pass the block every second or third beat.

In the well-known *Stannius experiment* a ligature is tied between the sinus and the auricles, and causes the auricles and ventricle to stop beating since the impulse can no longer pass from the one to the other. This is known as the Stannius heart. A second ligature, however, between the auricles and ventricle causes the ventricle to recommence beating at its own slow rate. The second ligature apparently acts as a mechanical stimulus by stretching the fibres, since a similar effect may be brought about by increasing the weight of the cardiographic lever or by injecting fluid through the aorta (Michael Foster). Section has a similar stimulating effect. Gaskell carried out similar experiments using a clamp instead of a first ligature.

In the mammal the foetal remnant of the sinus is called the sino-auricular node (Keith and Flack), and this acts as the **pace-maker** since its cells have a remarkable power of rhythmically discharging impulses. It is situated in the upper part of the sulcus terminalis near (in front) the entrance of the superior vena cava. If this part of the auricle is heated or cooled the heart-rate may be increased or decreased, but similar treatment of other parts of the heart does not produce this effect. It was indeed this fact which led to the discovery of the node. That the excitation-wave commences at the sino-auricular node has been fully demonstrated by Lewis by means of the string galvanometer which records the current of action of the heart. By placing electrodes on different parts of the heart he has shown that the electrical change occurs first at the node.

The starting-point in our knowledge of spread of the excitation-wave to the ventricle in the mammal was the discovery by Stanley Kent of bands of peculiar tissue passing across from auricles to ventricles. The principal one was subsequently and independently rediscovered and fully described by His, and is known as the auriculo-ventricular bundle or bundle of His. Some animals, especially when young, have relics of a right lateral bundle (Kent). The auriculo-ventricular bundle arises from the auriculo-ventricular node which is situated in the right auricle just in front of the coronary sinus. It runs forward in the lower part of the inter-auricular septum to reach the membranous portion of the inter-ventricular septum behind the tricuspid valve; here it courses along the upper border of the muscular part of the septum ventriculorum. The bundle divides into two main branches, right and left, one for each ventricle, that for the left penetrating the septum. The main branches continue towards the apex, branching as they go; their ramifications are connected with the network

of Purkinje fibres beneath the endocardium, which network is in turn connected with the main mass of ventricular muscle. The nodes and bundle are composed of modified muscle-fibres, intermingled with which are many non-medullated nerve-fibres, and are enclosed in a connective tissue sheath; they receive blood by special arteries. The bundle is particularly rich in glycogen. There is no special strand connecting the sino-auricular and auriculo-ventricular nodes; the wave of excitation initiated in the former spreads from it through the auricular muscle until it reaches the latter. The cells of the Purkinje tissue are peculiar in being striated only at their margins. They are large clear quadrangular cells with a granular protoplasm containing several nuclei, while the fibrillar continuity between the different cells is particularly well marked.

The conclusion that the auriculo-ventricular bundle is the important link which propagates the rhythmic wave was reached first by experiments on animals, and second, by observations in disease in man. In animals, cutting through the bundle abolishes the ordinary sequence of cardiac events. The auricles go on beating as a result of the stimulus of the node, but the ventricles beat at a slower rhythm. The stimulus for the ventricle is partly the rising venous pressure.

When the bundle is destroyed by disease in man there is a similar dissociation between the auricular and ventricular rhythm, the ventricles beating slowly and the auricles rapidly. This condition is known as **heart-block**, and in the early stages of the disease may be incomplete; then one out of every two or three auricular waves gets over to the ventricle, just as it does in Gaskell's experiments on the frog's heart when the clamp is not sufficiently tight.

Such observations throw a good deal of light on the propagation of the normal heart-wave. The view generally held is that the wave starts in the sino-auricular node, and spreads thence to both auricles; it is picked up by the ventricular node of Tawara and travels to the ventricles by the auriculo-ventricular bundle, reaching first the papillary muscles, and thence the rest of the heart until it arrives at the apex; finally it returns to the base of the heart in the region of the origin of the pulmonary artery, which is the representative of the bulbus aortæ in the primitive heart.

The Histology of Cardiac Muscle.

This has been referred to on page 50. The important point to emphasise is the intimate connection of all cardiac muscle cells with each other. This produces a syncytium which acts as a whole.*

* It seems probable that this syncytium is not so complete in the mammal as in the frog, for it has been found that a part of the heart may not contract if a branch of the auriculo-ventricular bundle is injured.

The Properties of Cardiac Muscle.

1. **Rhythmicity** is a fundamental property of the cells of cardiac muscle, and may be observed in a single cell when the cell has been grown outside the body in tissue culture (Carrel).

2. The fact that the Stannius heart is quiescent has enabled physiologists to study the properties of heart muscle. When the heart has been stopped for a little while and is stimulated artificially it shows a **staircase phenomenon**; that is to say, with the *same* strength of stimulus the first few contractions increase in size. This is the same as the "warming up" effect seen in voluntary

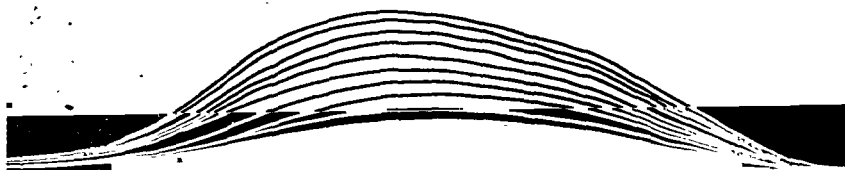


FIG. 54.—Staircase from frog's heart. This was obtained from a Stannius preparation; an induction shock being sent into it with every revolution of the cylinder (rapid rate). The contractions became larger with every beat. To be read from right to left.

muscle, but in the heart it is better marked. It must not be confused with increased contraction in striped muscle due to increased strength of stimulus.

3. **The "all or none" phenomenon.**—By this is meant the fact that the amount of contraction does not vary with the strength of the stimulus. A stimulus strong enough to produce a contraction causes a maximum contraction, because as we have seen the cells of cardiac muscle are not separate like those of voluntary muscle, but are all linked together and act as a single muscle-fibre.

4. **Refractory Period.**—The heart-muscle has a long *refractory* period; that is to say, after the application of a stimulus, a second stimulus will not cause a second contraction until after the lapse of a certain interval. The refractory period lasts as long as the contraction period and on this account the heart-muscle can never be thrown into complete tetanus by a series of stimulations. The refractory period can also be shown in a normally beating heart. If the heart is stimulated during systole no change is observed, but if the stimulus is applied during diastole, an *extra systole* is produced. If the normal stimulus from the auricle reaches the ventricle during this extra systole, it produces no effect and the heart appears to have missed a beat. This is known as the *compensatory pause* (fig. 55).

Missed beats in man are commonly due to similar extra systoles which may be too small to be felt at the pulse but which may be heard by the stethoscope or demonstrated by the electro-cardiograph. The beat following the extra systole may be unduly large since the heart is filled with extra blood during the prolonged diastole.

The importance of the refractory period becomes apparent when, for one reason or another, a source of stimulation occurs in the heart in addition to the normal sinus beat. Whether or not this extra stimulus will excite the heart depends on the excitability of the heart at the time such a stimulus arrives. Sometimes such

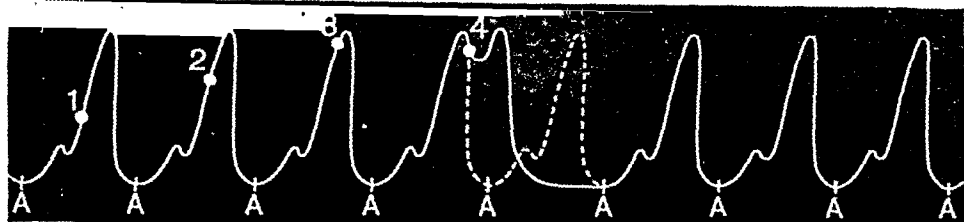


FIG. 55.—Record of frog's heart. For convenience the points of stimulation (shown by numbers) are shown in consecutive heart-beats, but this would scarcely be possible in an actual experiment. (See text.) The normal stimulus of the sinus to the auricle is shown at A.

extra stimuli cause the auricle to contract either at great speeds or very irregularly. These conditions are respectively known as auricular flutter and auricular fibrillation and are important clinical conditions.

Auricular Flutter.

Auricular flutter is a very rapid contraction of the auricle which depends on the properties of cardiac muscle.

If a ring (fig. 56 A) of cardiac muscle is stimulated by an induction shock at *a*, the wave of excitation started there travels in the direction of the two arrows until they meet at *b* (B, C, D in figure), and when the two crests meet the whole ring is in the contracted state (dark shading). While it is contracted it is irresponsive to a second stimulus (refractory period). It then recovers in the same order and direction as shown in E, F, G, H, until the whole ring is once more responsive as shown by the absence of shading. If successive stimuli are applied, each one will elicit the same train of events, provided the time between the stimuli is sufficiently long for recovery to take place. If a second stimulus occurs when the ring is in the state F, a fresh wave may be propagated at *a*, before the response to the first stimulus has subsided at *b*. In these circumstances two waves will be moving through the ring as shown in fig. 57, I, J, K. Suppose next that the successive stimuli are thrown in at smaller intervals, the second wave may start well enough at *a*, and travels at first freely in both directions as before, but if recovery in the two halves of the ring is different, in one half the wave reaches a point where the muscle is still refractory and so stops, but in the other half complete recovery may have occurred; this wave will go on, and be able to get all the way round the ring, for by the time it arrives at the point which stopped the first wave, refractoriness will have disappeared there; this single wave gets back to its starting-point, finds this muscle has also recovered and continues its course round and round the ring, a wave which has no ending. In this way the last stimulus of a series, the rate of which is carefully controlled, will initiate not a single contraction but a series of contractions. This is what is called *circus*

movement, a wave of response which travels continuously through a re-entrant path of muscle. It may in experiments last for hours. The rate of *auricular flutter* in man, as it is called, may rise to 230 to 250 per minute. In the more serious state of fibrillation the rate may be much greater. The value of the experimental circus movement is that it enables one to investigate the meaning of circus movement in disease.

Flutter is due to continuously circulating waves, with centrifugal offshoots into

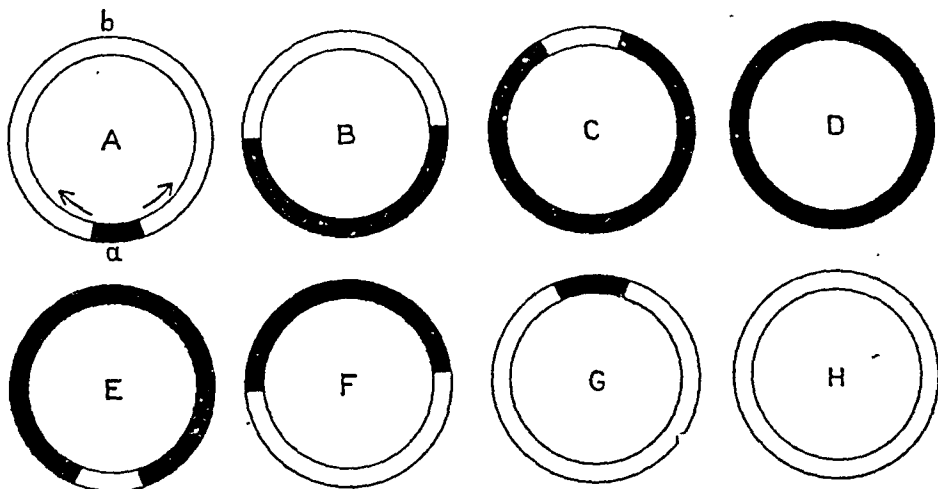


FIG. 56.—The ring experiment. (After Lewis.)

the rest of the cardiac tissue, and in man it has been seen to continue unceasingly for many years. In order that the wave may be continuous, and always find the muscle it enters in the responsive state, the duration of the refractory period at any given point must always be less than the time spent by the travelling wave in completing its circuit, and this time will depend on two other factors, namely, the length of the circuit and the rate of travel. Treatment of the condition of flutter

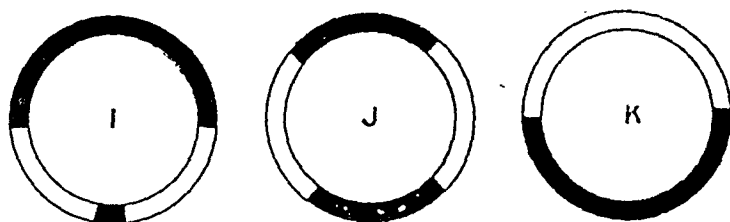


FIG. 57.—The ring experiment. (After Lewis.)

consists in administering a drug which increases the rate of conduction and the duration of the refractory phase so that the muscle has not yet recovered its excitability by the time the excitation arrives. The drug which has so far been found most satisfactory is quinidine.

Auricular fibrillation is a condition of the auricles arising from severe damage to the auricular muscle in which its ordinary rhythmical contractions are replaced by grossly irregular and fibrillar contractions of individual or groups of fibres. The auricles cease to function and the ventricles are filled solely as a result of the venous pressure. The auricular irregularity leads to great irregularity of the ventricles.

Ventricular fibrillation.—This is incompatible with life and occurs commonly at the point of death. In this condition the ventricle instead of contracting as a whole contracts and twitches irregularly in different parts at the same time and ceases to act as a pump. Fibrillation is the cause of sudden death from an electric current. Immediate cardiac massage or the injection of calcium and potassium may bring about recovery in some instances if the damage is not too severe.

The Electro-Cardiogram.

The muscular tissue of the heart gives rise on action to an electrical disturbance which is in all essential features the same as the diphasic variation we have already studied in connection with voluntary muscle. The excised beating heart of a frog can be readily connected either to a galvanometer or an electrometer; a simple diphasic variation is recorded.

It is, however, possible (as Waller first demonstrated) to obtain an electro-cardiogram in man if each hand is placed in a basin of salt solution connected to an electrometer.

Since the heart-muscle is not a simple longitudinal strip like a sartorius there is great complexity in the electrical record of the intact organ. Thus Bayliss and Starling described in the mammalian heart a triphasic variation, which Gotch has shown to be explicable in the following way. Leaving out of account complications due to auricular activity, he has shown that the contraction process in each ventricle and its electrical concomitant commence at that part of the base of the ventricle at which it is continuous with its respective auricle; the contraction-wave travels to the apex and returns to the part of the base from which the aorta on one side and the pulmonary artery on the other side arise. An electrode placed on the base will therefore record the increased galvanometric negativity at the beginning and at the end of the ventricular contraction; the electrode on the apex will record the middle phase when the contraction-wave reaches that point and causes an increase of galvanometric negativity there.

Records are usually taken with the string galvanometer but an oscillometer may be used. In electro-cardiography (fig. 83) the electrodes consist of vessels of saline solution into which the hand or foot is placed and in each of which there is a zinc electrode in a porous pot of zinc sulphate. Such an electrode prevents polarisation (see p. 35). In clinical work it is customary to take records from three different sources or "leads." Lead I consists of the two hands, lead II of the right hand and left foot (axial lead), and lead III of the left hand and left foot. The different leads furnish information on the comparative activity of the two sides of the heart.

From what has been said in relation to conduction in the heart, we are in a position to understand the causation of the individual waves. The size of each varies considerably even in health, but in heart disease the electro-cardiogram shows very marked differences from the normal.

The waves on the electro-cardiogram are explained as follows. The wave P, due to auricular activity, is followed by a pause before the waves which accompany ventricular systole occur. During this pause it is supposed that the excitatory-wave is travelling along the auriculo-ventricular bundle, the mass of which is too small to affect the galvanometer. The remaining waves accompany ventricular activity; the final wave T indicates the arrival of the contraction-

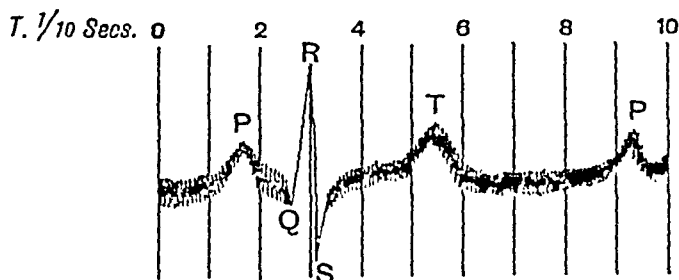


FIG. 58.—Electro-cardiogram obtained by photographing the movements of the thread of a string galvanometer. The electrodes were connected to two vessels of salt solution, in one of which the right hand of a man was placed; this would lead off the base of the heart: in the other his left foot was placed; this would lead off the apex of the heart. Waves upwards indicate that the base is galvanometrically negative to the apex; downward waves have the opposite meaning. Wave P accompanies auricular systole; waves Q, R, S, and T occur during ventricular systole. The time-tracing (T) shows tenths of a second.

wave at the base. Different observers differ greatly in their interpretations of the waves Q, R, S.

According to Lewis, the excitation-wave starts in the septum of the ventricles, travels down this to the apex, and from the latter up the lateral wall to the base. Throughout this passage the electrical axis constantly changes, and it is this change which is responsible for the complexity of the electro-cardiogram. The deflection R represents the negativity of the lead from the right upper limb; this is produced not by activity of the base, but by the active process passing down the septum before there is activity either at apex or base; the deflection S is produced after the active change has finished in the septum and at the apex, that is to say, it is produced by activity at the base. Yet this deflection S represents relative negativity of the lead from the left lower limb.

An important feature of the electro-cardiogram is that it gives definite information regarding the rate of the auricle compared with that of the ventricle, and the time taken for the impulse to pass down the auriculo-ventricular bundle, as indicated by the PR interval. The polygraph (see p. 140) is used for a similar purpose.

Frequency of the Heart's Action.

The heart of a healthy adult at rest contracts 50 to 80 times in a minute; but many circumstances cause this rate to vary even in health. The chief are age, temperament, sex, food and drink, exercise, time of day, posture, atmospheric pressure, temperature.

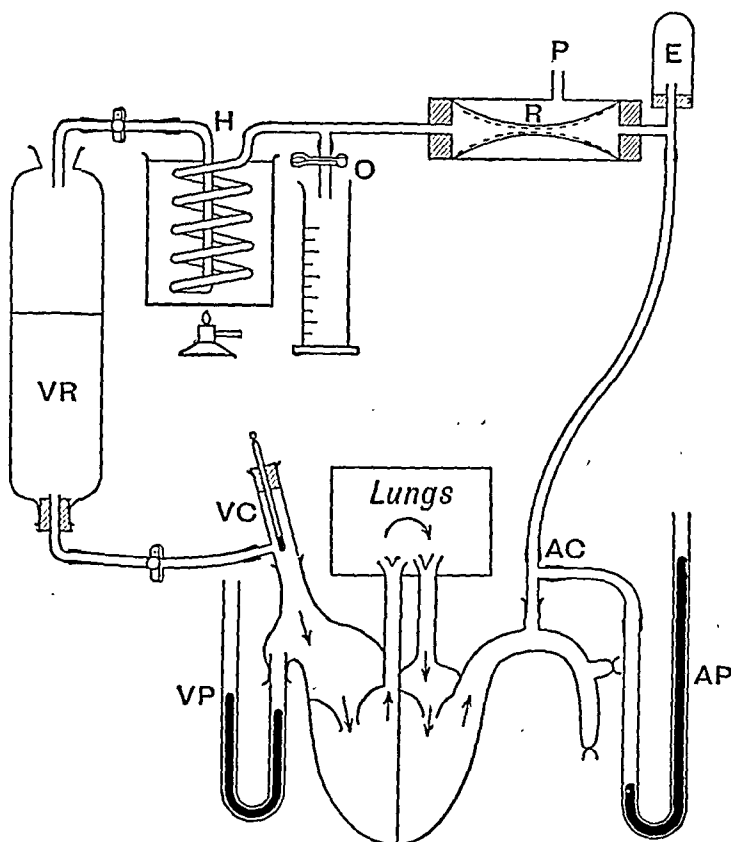


FIG. 59.—Knowlton-Starling heart-lung apparatus (after Hemingway). AC, arterial cannula; E, air-chamber, to give elasticity; H, heating apparatus; O, outlet for determination of output (when determining output this clip is opened for a given time and outlet to venous reservoir closed); P, to pressure-bottle; R, peripheral resistance (dotted line shows position during increased resistance); VC, venous cannula; VR, venous reservoir; VP, manometer to record venous pressure (regulated by screw clip on tube from reservoir); AP, manometer to record arterial pressure.

In regard to other animals than man, it may be stated generally that the smaller the animal the more rapid the heart-rate since the metabolic rate in small animals is much greater than in large animals. (See Metabolism.)

The frequency of the heart's action gradually diminishes from the commencement to near the end of life, thus:—

Before birth the average number of pulsations per minute is	150	About the seventh year	from 90 to 85
Just after birth	from 140 to 120	About the fourteenth year	85 to 80
During the first year	130 to 115	In adult age	80 to 50
During the second year	115 to 100	In old age	70 to 60

In health there is a uniform relation between the frequency of the heart-beats and of the respirations; the proportion being 1 respiration to 4 or 5 beats. The same relation is generally maintained when the action of the heart is naturally accelerated, as after food or exercise; but in disease this ratio may be upset. The rate of the heart depends on the pace-maker, which, as we shall see later, may vary its activity especially in relation to exercise.

The Output of the Heart.

It is evident that the output of the heart is of the utmost importance in maintaining the circulation. Since the output of the heart indicates the rate of the circulation and is presumably determined by the needs of the body in relation to the supply of oxygen, its estimation, if a convenient and trustworthy means could be found suitable for man, might be of value in determining not only the needs but also the adaptation of the circulation in pathological conditions.

Several methods for the investigation of the cardiac output of animals have been devised, but in actual practice only a few have been generally retained.

The Heart-Lung Preparation (Knowlton and Starling).—This method consists essentially of cutting out the systemic circulation by joining a branch of the aorta to the superior vena cava, all the other systemic arteries and veins being tied off. In this way all possible variables outside the heart may be accurately controlled. In order to prevent the blood flowing with abnormal freedom from the artery to the vein and to maintain a pressure in the system (see Blood-Pressure), an artificial variable resistance in the form of a readily compressible tube is introduced, while elasticity is also given to the artificial system—to simulate natural conditions. The output of the heart may readily be measured by allowing the blood to collect for a measured period of time in a cylinder beyond the resistance. A diagram of the apparatus is shown in fig. 59.

The value of this method lies in the fact that the filling of the heart and the peripheral resistance can be controlled. It gives therefore valuable information regarding the heart isolated from the rest of the body.

Cardiometer Method.—In the intact circulation the method which is adopted is that introduced by Roy. The heart is placed in an air-tight chamber connected with a piston recorder (fig. 60). During diastole the heart takes up more space and a corresponding amount of air is driven into the recorder. The recorder is standardised subsequently by running fluid into it from a burette and a measure is thereby obtained of the output per beat. By counting the beats

and multiplying the number by the output per beat we find the output per minute (fig. 61).

The method is of special value in ascertaining whether or not a change in arterial pressure, say, due to a drug, is due to a change in the output of the heart.

In this way it can be demonstrated that the output of the heart depends primarily on the *venous inflow*, *i.e.* the amount of blood entering the heart in diastole, and that, quite apart from changes in rate, the heart is able to vary its output and the work it does according to requirements. This it does in virtue of the fact

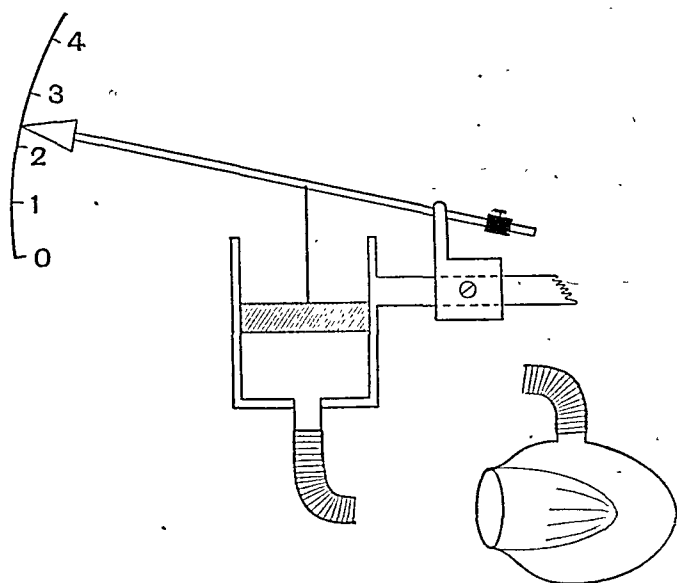


FIG. 60. — Cardiometer—composed of piston recorder (Ellis) and heart chamber. The chamber is made of glass. One opening leads to the recorder and the heart is inserted into the other. In some forms the latter has a thin rubber diaphragm which has a hole in the centre and which fits accurately round the base of the heart, but in other forms the heart fits into a thin rubber sheath (as shown) which does not impede its action. For longer records the rubber is perforated at the apex and the chamber has an inferior opening by which pericardial fluid may be drained away (Hemingway).

that the greater the initial length of the fibres, *i.e.* the greater the filling, the more forcible their contraction. This has been called by Starling (1918) **the Law of the Heart**, but it is applicable to muscle generally. Starling was Professor of Physiology at University College, London.

A rise in blood-pressure within normal limits caused by increasing the resistance (R in fig. 59) makes no difference to the output except for a few beats. At first the heart fails to drive out its contents adequately, but if the venous inflow is maintained this is added to the retained blood to distend the ventricles which consequently contract more forcibly and overcome the resistance. This is an important provision in the mechanism of the heart since there is

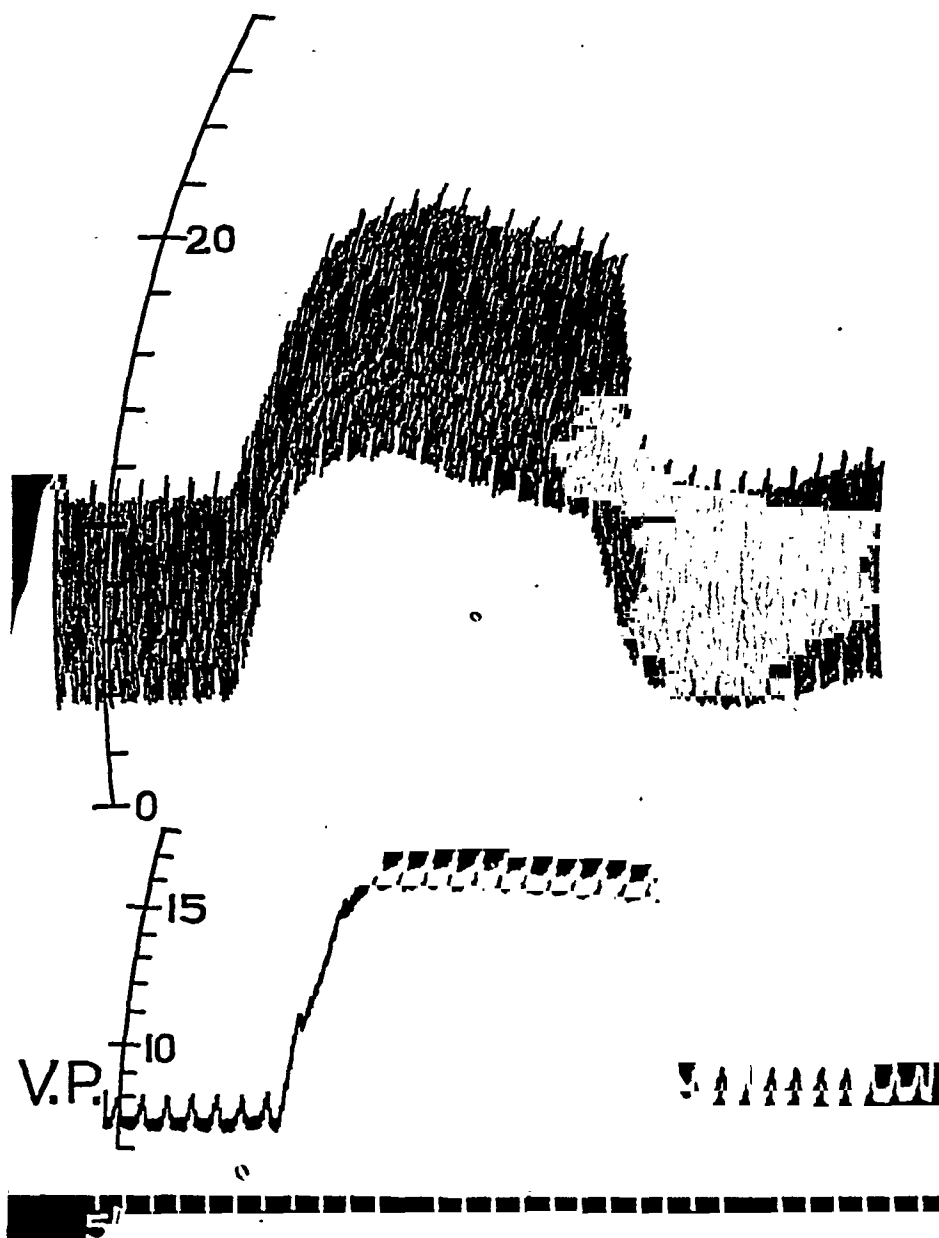


FIG. 61.—A record showing the effect of the venous pressure on the output of the heart. A raising of the venous pressure causes a marked increase in the output per beat and per minute. (See text.) The upper tracing is a cardiometer record, the lower a record of venous pressure in a heart-lung preparation (by Hemingway). To study the rate of change in the heart-volume during a single beat an optical record is necessary.

an increased resistance during exercise when it is important that the output should be maintained or increased.

The rate of the heart makes no difference to the output if the

venous inflow is low; but if this is reasonably high, as it usually is in the body, a change in the rate modifies the output. The reason for this is as follows: The heart increases its rate by shortening diastole, but it is evident that such shortening may have the effect of decreasing the time for filling. When the venous inflow is low, or the heart-rate very fast, this is actually so, with the result that, although there may be an increased number of beats, the output per beat may be diminished and the output per minute may therefore be unchanged or even reduced. On the other hand, when the venous inflow is of normal amount, the heart fills in the early part of diastole and a shortening of the latter does not therefore seriously reduce the filling per beat. Since the output per beat is unchanged, an increased rate increases the output per minute. These facts may readily be demonstrated in an animal. If the blood-pressure is recorded and the rate of the heart varied by heating the pace-maker, a rise of blood-pressure results. On the other hand, if the animal is bled sufficiently (a procedure which, for reasons described later, lowers the venous pressure) such a variation of the heart-rate makes no difference to the blood-pressure.

These facts can, however, really be inferred from a study of the volume changes in the heart taken by means of a cardiometer (fig. 60). In the intact animal it is evident that the venous inflow will depend on the **venous return**. This is discussed later.

These facts have a considerable practical importance since in disease such as hyperthyroidism the heart-rate may reach 180 per minute. It has been found that the diastolic volume of the heart begins to decrease slightly at 80 per minute, but the increased rate maintains the output until 120 is reached. In exercise the reduction of diastolic volume is prevented by the increased venous return which occurs at the same time as the cardiac acceleration.

In man it is obvious that such methods cannot be used and, unfortunately, no convenient trustworthy method is yet available. Probably the method of Douglas and Priestley is the best. The amount of carbon dioxide in 100 c.c. of venous blood is estimated and compared with that in 100 c.c. of arterial blood. The difference, normally about 4 c.c., is that lost by 100 c.c. in passing through the lungs when the body is at such rest as is obtainable under experiment. By finding the total amount of carbon dioxide given off in a given time, we can arrive at the number of c.c. of blood which must have passed through the lungs to have lost this amount of CO_2 . This amount really represents the output of the right ventricle which is the same as that of the left. For example, if a man gives off 225 c.c. of carbon dioxide per minute and each 4 c.c. is given off

in the lungs by 100 c.c. of blood, then 5625 c.c. of blood per minute must have flowed through the lungs. The difficulty in the method lies in obtaining a sample of mixed venous blood. This is necessary as the venous blood from different parts of the body contains different amounts of carbon dioxide and oxygen. In animals a sample of the mixed venous blood may be obtained by a needle plunged into the right ventricle, but in man this is not generally risked, although it has been done in Germany. Good results have, however, been obtained by passing a catheter down the jugular vein to the right auricle (Richards and others). This appears to be a safe procedure.

Another and more usual method of obtaining the CO_2 content of the mixed venous blood in man is indirect and described in relation to Respiration.

A *rough* estimate of the cardiac output can also be obtained from our knowledge of the oxygen content of the mixed venous blood by finding the amount of oxygen taken in by the lungs per minute and calculating the amount of blood which must have passed through the lungs to have taken up this amount of oxygen (Fick). In this calculation it is assumed that in order to convert the mixed venous blood into arterial blood, 5.5 c.c. of oxygen should be taken up by 100 c.c. of blood. Several other methods depend on a similar Fick principle but an abnormal gas is used, *e.g.* nitrous oxide (Krogh), ethyl iodide (Henderson), of which the solubility in blood is known.

In a fasting man at rest the cardiac output, *i.e.* of each ventricle, is estimated at about 3 to 5 litres per minute, but in severe exercise it may be increased to over 30 litres per minute—a most remarkable performance for such a small organ.

The output of the heart is increased when food is taken and may be doubled by a heavy meal.

The output of the heart it is obvious must, other factors being equal, depend on the efficiency of the heart as a muscular pump.

The power of the heart to increase its output is called the **cardiac reserve**, and is of considerable clinical importance. It is appreciably reduced in cardiac disease because some of the reserve is utilised in overcoming the pathological defect, *e.g.* disease of a valve, or of the cardiac muscle; less is therefore available for exercise, and symptoms of cardiac impairment, *e.g.* breathlessness on slight effort, are produced. In severe cases all the reserve is used up and exercise is impossible. In less severe cases the amount of exercise which can be done without discomfort is a measure of the cardiac efficiency.

In addition to this immediate power of adapting itself to requirements, the heart, like any other muscle, undergoes considerable hypertrophy (increase of muscular substance) if increased work is done for a considerable time. This is of great importance in practical

medicine, since in valvular disease of the heart, when a valve is leaking or obstructed, the efficiency of the heart depends on its power to compensate in this way.

The hypertrophied cardiac muscle if healthy continues to be capable of driving out the contents of the ventricles in spite of the failure of the valves—provided this is not too great and time is allowed for the muscle to adapt itself to the extra work.

In conclusion, it may be pointed out that the mere determination of the output of the heart gives very little exact information regarding the cause of any change in blood-pressure such as might be produced by a drug, as the output depends on two factors, the venous filling and the cardiac efficiency, each of which may vary independently. Thus a diminished output of the heart might be produced by a drug which increased the capacity of the circulation, lowered the venous pressure, and reduced the cardiac filling.

The Pericardium.

This we have seen is a sac enclosing the heart. The pericardium consists of two layers, one fibrous and one serous. The inner serous layer becomes continuous with the serous covering of the heart or *epicardium*; the outer fibrous layer of the pericardium is attached below to the diaphragm, the partition between the thorax and the abdomen. The sac formed by the junction of the serous layer of the pericardium and the epicardium contains just enough lymph (pericardial fluid) to lubricate the two surfaces and enable them to glide over each other smoothly during the movements of the heart. The presence of numerous elastic fibres in the epicardium enables it to follow without hindrance the changing shape of the heart itself; but the parietal layer of the pericardium, surrounded as it is by a fibrous layer (fibrous pericardium), appears to be inextensible, and so limits the dilatation of the heart. Its obvious function is to prevent over-distension of the heart, since if the organ is filled beyond a certain limit its fibres will act at less mechanical advantages; but since it has been found, post mortem, that the pericardium may have been absent or seriously ruptured without serious symptoms before death, it has been suggested that its function is to prevent the heart from changing its position with changes in posture. It has been shown by Biljsma, however, that the pericardium plays an important part in limiting the size of the heart and in preventing it from being over-distended in exercise. He has shown that the response to increased filling is diminished if the pericardium is removed.*

* If on the other hand the pressure in the pericardium is very slightly increased a serious interference with cardiac filling occurs and may result in death in man.

When the cardiac valves are diseased and the heart becomes enlarged the pericardium necessarily enlarges also as a result of *sustained* stretching.

Work and Gaseous Exchanges of the Heart.

The heart's work consists in discharging blood against pressure and in imparting velocity to it. The former will clearly depend on the output of the heart and on the various factors which influence blood-pressure, the latter on the blood-pressure. Without going into the somewhat elaborate calculations obtained from these and other data, it will be sufficient to say that $\frac{1}{10}$ of the total energy of the heart is used in imparting velocity to the blood, but when the blood reaches the aorta the velocity is so checked that the kinetic energy of the blood in the aorta is only about $\frac{1}{800}$ of the total imparted by the heart.

It will be observed that the work done by the right side of the heart is very much less than that done by the left, but when there is disease of the mitral valve the right ventricle is increased in size, and its work approximates that of the left.

On the work of the heart depends its gaseous exchange.

Gaseous Exchanges in the Heart.—The using up of oxygen by the living heart was well illustrated by an old experiment of Yeo's. He passed a weak solution of oxyhæmoglobin through the excised beating heart of a frog, and found that after it had passed through the heart, the solution became less oxygenated and venous in colour.

This is still better shown by Barcroft and Dixon who estimated the gases in the blood entering and leaving the coronary vessels of a cat. It was found that the metabolism in the heart tissue was reduced during vagus inhibition; this was followed by increased metabolism during the subsequent period, which corresponds to the increase of visible activity which then occurs. Similar results were obtained by Lovatt Evans on the heart-lung preparation of the dog. He found that the oxygen usage was varied with the output of the heart and the diastolic blood-pressure against which it had to be expelled, *i.e.* the work done by the heart.

It is possible by studying its gaseous exchange to arrive at an idea of the efficiency of the heart. This has been done by Evans on the heart-lung preparation. It has been shown that the oxygen consumption of the heart bears a direct relationship to its diastolic volume, that is, with a constant heart-rate the oxygen consumption may be increased by merely increasing the filling. There is, however, a point of maximum efficiency beyond which the oxygen consumption rises out of proportion to the output.

Since, as is evident from the experiment quoted above, a change in the heart-rate affects its oxygen consumption, it is of interest to remark that there is evidence which indicates that it is more economical for the heart to increase its output per minute by greater work per beat than by an increased rate. This fact illustrates the importance of the nervous cardio-inhibitory mechanism, which prevents the heart from beating any faster than is necessary for a given inflow.

The Nutrition of the Heart.

In the lower vertebrates, *e.g.* the frog, the heart is nourished directly from the blood passing through it, but from the reptiles

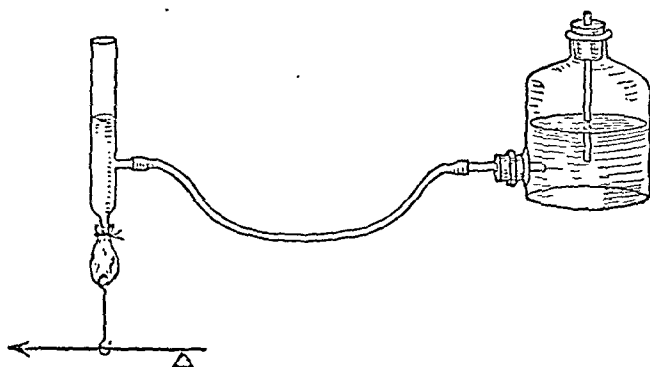


FIG. 62.—Perfusion by Symes' cannula.

onwards there is developed a special blood-supply in the form of the coronary vessels.

Ligature of the coronary arteries causes almost immediate death; the heart, deprived of its normal blood-supply, beats irregularly, goes into fibrillary twitchings, and then ceases to contract altogether.

If a frog's heart is simply excised and allowed to remain without being fed, it ceases to beat after a time varying from a few minutes to an hour or so. But if it is fed with a nutritive fluid, it will continue to beat for many hours. Drugs may be added to the perfusion fluid, and their effects noted. The fluid may be passed through the heart. The frog's heart, it should be remembered, possesses no coronary vessels; the spongy texture of the cardiac tissue enables it to take up what it requires from the blood in its interior. The fluid may be caused to flow into the heart from the aorta or the vena cava and a record taken from the apex in the usual way.

A simple method is that of Symes, in which the heart is made to move a lever by means of a hook in the apex; in this case the cannula is a simple one and is introduced into the auricle.

The best nutritive fluid to employ is undoubtedly the natural

fluid, the blood. But in order to use blood there are practical difficulties; it is difficult, for instance, to obtain much blood from a frog; it is difficult to prevent it from clotting, and if agents are added to check clotting, such agents usually act deleteriously on the cardiac tissue. The blood of another animal may not be altogether innocuous, and this is specially the case if that blood has been previously whipped, and the fibrin removed. It was, however, found by Ringer that a solution of the inorganic salts of sodium, calcium, and potassium in the proportions occurring in the blood will maintain cardiac activity for a long time without the addition of any organic material. (This is known as **Ringer's solution**.) These salts are not nutritive in the strict sense, but they constitute the stimulus for the heart's action. Howell has shown that such an inorganic mixture is especially efficacious in throwing the sinus or venous end of the heart into rhythmical action. The normal stimulus for the starting of the heart-beat is thus to be sought in the mineral constituents of the blood. These mineral compounds in solution are broken up into their constituent ions; and of these, sodium-ions are the most potent in maintaining the conditions that lead to irritability and contractility. A solution of pure sodium chloride, however, finally throws the heart into a condition of relaxation; and it is necessary to mix with it small amounts of calcium-ions to restrain this effect. Potassium is not absolutely necessary, but it favours relaxation during diastole. Calcium, on the other hand, is the element which produces and is necessary for contraction, and if present alone or in excess, will produce an extreme contraction known as *calcium rigor*.

The Excised Mammalian Heart.—The mammalian heart can also be kept alive and active after it has been excised. Its usefulness not only in reference to the metabolism occurring during normal cardiac activity but also from the pharmacological point of view, is obvious.

In order to maintain the action of the excised mammalian heart, certain precautions must be taken—

1. The perfusion fluid must be at or about body temperature (37° - 39° C.).
2. It must circulate through the coronary vessels.
3. It must be well oxygenated.

As before, living blood is the ideal fluid for perfusion, but the practical difficulties in its use are so great, that a modification of Ringer's fluid is usually employed. On this fluid the heart will continue to beat for many hours, but it will beat longer (sometimes several days) if a little glucose is added to the solution. We owe this modified fluid, and the oxygenation alluded to above, to Locke;

the perfusion fluid now universally employed is called **Ringer-Locke's solution** and has the following composition:—

Pure distilled water *	100 c.c.
Sodium chloride	0.9 gramme
Potassium chloride	0.042 "
Calcium chloride	0.024 "
Sodium bicarbonate	0.02 "
Glucose	0.1 "

Locke investigated other sugars besides glucose, but no other

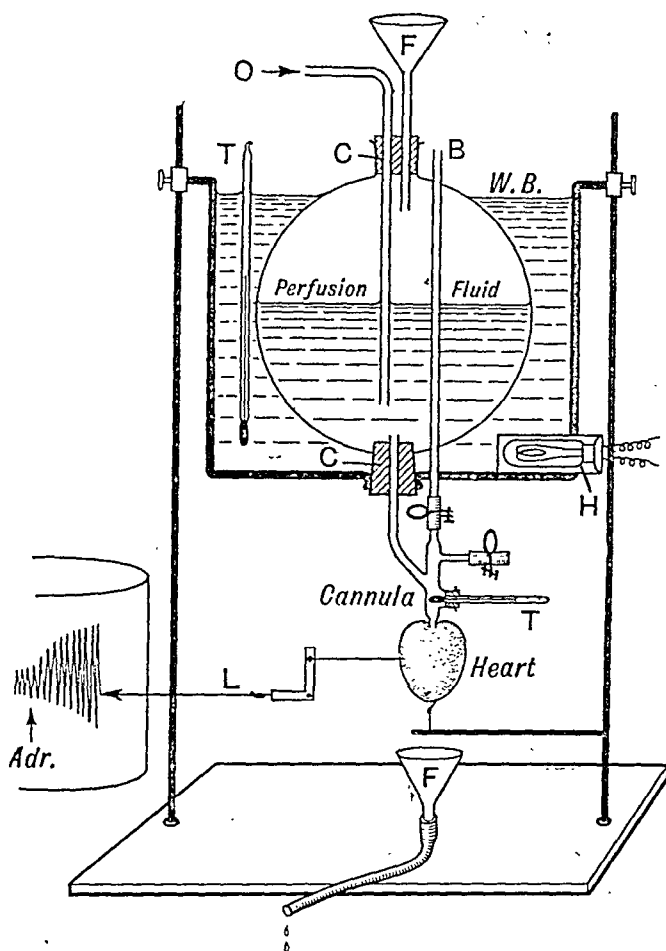


FIG. 63.—Apparatus for perfusion of the mammalian heart. Warmed perfusion fluid is poured through F into the large glass flask, oxygenated by bubbling oxygen through it from O and kept warm by the water-bath heated by the lamp H. A tube passes through the cork C in the bottoms of the flask and bath and conveys the fluid to the heart. B, which is outside the bath, indicates conveniently the amount of fluid in the flask when the clip is opened. T = thermometer. L = writing lever applied to drum.

has the same favourable effect; fructose is better than most other sugars, but not nearly so good as glucose.

* Freedom from metals and distillable products is essential.

A mammal such as a cat* or rabbit is killed by bleeding or pithing. The heart enclosed in the pericardium is quickly cut out, and gently kneaded to free it from blood in some warm Locke's solution. The pericardium is then dissected off, and a cannula tied into the aorta; this is connected to a burette which is kept full of Locke's solution. The solution is maintained at body temperature by a warm water-jacket, and is well oxygenated by letting oxygen bubble through it. The fluid is then allowed to flow; its pressure closes the aortic valves, and so the fluid enters the coronary arteries, and escapes from the right auricle, which should be freely opened. Under these conditions the heart will continue to beat for many hours. A graphic record may be obtained by putting a small hook into the apex, and attaching this by a thread to a recording lever beneath it. A very good illustration of the usefulness of the method for demonstrating the action of drugs consists in adding a small amount of chloroform to the circulating fluid: one notices its immediate depressant effect; on the other hand, a minute dose of adrenaline markedly increases the rate and force of the heart.

The Coronary Circulation.—The heart normally is nourished by blood which supplies its muscle by way of the coronary arteries. This circulation is dealt with later.

The Nutrition of Blood-Vessels and of Tissues generally.

The smaller blood-vessels are nourished directly by their contents but the larger vessels with thick walls have minute vessels running into their substance. These are known as the *vasa vasorum*.

What has been said of the heart pertains also to blood-vessels. In order to keep blood-vessels alive after the animal has died, and in a state to respond to drugs, they must be bathed in some such solution as Ringer's. For most purposes a fluid containing about a quarter the calcium in Ringer's solution gives good results. Rings may be cut from a large vessel and attached to a delicate lever, or the fluid may be passed through the vessels under pressure and the rate of flow or the resistance to the flow measured. It can be shown in this way that calcium is as essential for the contraction of smooth muscles as it is for the heart.

It is certain that all tissues require similar nourishment, but some need more oxygen than others and some, such as nerve-cells, are exquisitely sensitive to changes in hydrogen-ion concentration. Hence it is extremely difficult to keep the central nervous system alive after the normal blood supply has failed. For this reason the

* For the cat less calcium is often an advantage.

nervous system dies extremely rapidly at death. The power of recovery of the different parts of the brain has been investigated by shutting off the blood supply, and it has been found that the higher parts are the first to suffer permanent damage as indicated by their failure to recover.

For sustained nutrition many other elements are necessary to repair worn-out tissue. The substances necessary to effect such repair are discussed later in the section on Metabolism.

REFERENCES.—On the output of the heart, Bainbridge, Starling, Grollmann.

CHAPTER XIII

THE CIRCULATION IN THE BLOOD-VESSELS

THE movement of the blood from the heart through the arteries, capillaries, veins, and back to the heart, depends on the head of pressure produced by the pumping action of the heart. In the succeeding pages we shall see how the intermittent movement imparted to the blood is converted into a constant flow through the delicate capillaries, and why the arterial blood-pressure is kept up while the heart is filling.

The blood-pressure has the same purpose as the pressure in gas- or water-mains, namely, it ensures adequate distribution in varying circumstances and, as we shall see, should it fall in man below a certain critical level serious consequences ensue.

The Arterial Blood-Pressure and its Maintenance.

For purposes of description it is convenient to enumerate first the factors which maintain the arterial pressure. These are:—

1. The volume of the blood pumped out by the heart.
2. The peripheral resistance to the flow of blood from the arteries.
3. The elasticity of the blood-vessels.

In order that we may understand blood-pressure, it is necessary to consider some of the general **laws of fluid pressure**.

Let us consider the simple case of a fluid flowing from a reservoir, R (fig. 64), along a tube, which is open at the other end.

In the course of the tube a number of upright glass tubes are inserted at equal distances. The upright tubes which measure the lateral pressure exerted by the fluid on the wall of the main tube, are called *manometers*. Between C and D, a tap T can be opened or shut at will. If the tap is closed there will naturally be no flow of fluid, and the fluid will rise to equal heights in the upright tubes A, B and C.

If now the tap is opened slightly, the fluid flows on account of the difference of pressure brought about by gravitation; the height of the fluid in the manometers indicates that the pressure is greatest in R, less in A, less still in B, and least of all in E.

On account of the resistance of the tap, the difference between

D and C is much more marked than the difference between B and A. If the fluid which flows out of the end of the tube is collected and poured back into R, we complete the circulation.

The model serves to illustrate an important factor in the maintenance of the blood-pressure, namely, the **peripheral resistance** to the flow of blood from the arteries. This may be varied by means of the tap T; if the tap is tightened, one imitates increased constriction of the peripheral vessels; if it is loosened, one imitates dilatation of the vessels. If the tap T is not quite closed, the arterial pressure (in A and B) rises, and the venous pressure (in

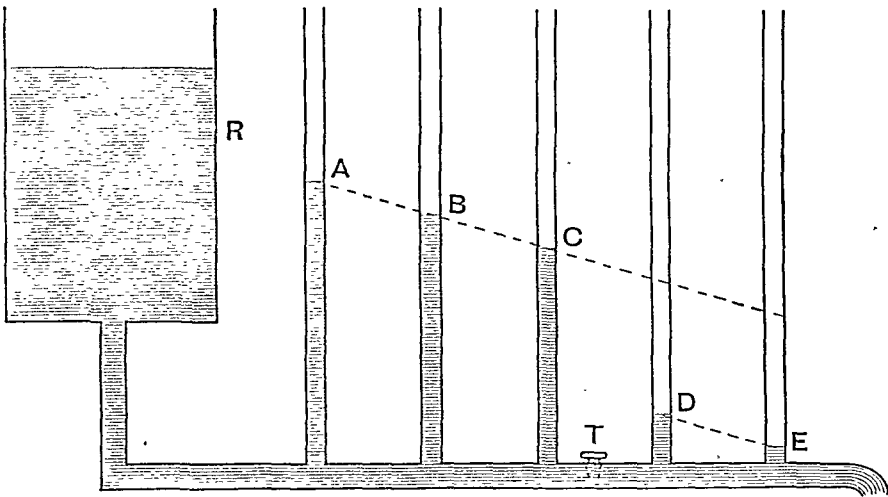


FIG. 64.—Model to illustrate the effect of peripheral resistance.

D and E) falls. If it is closed entirely, the fluid in A and B rises to the same level as that in R; the pressure of R is not felt at all by D and E, which empty themselves, and the flow ceases. If the tap is freely opened, the arterial pressure falls, and the venous pressure rises.

Measurements of the blood-pressure in various vessels indicates that the main peripheral resistance is in the region of the arterioles; but since the capillaries are not all open in a resting tissue they must also contribute largely to the resistance. The truth of this assumption has been demonstrated when the arterioles are dilated; the dilatation of the capillaries by the drug histamine causes a diminution of the peripheral resistance (Dale and Richards). The peripheral resistance or frictional resistance to the blood-flow depends on the calibre of the peripheral vessels and the viscosity of the blood. The former, however, varies very much from time to time.

How the peripheral resistance and the **elasticity of the vessels**

act together to maintain the pressure between the heart-beats, that is the **diastolic pressure**, may readily be shown by the model represented in fig. 65.

The heart (H) is represented by bulb syringe with valves (V) which is worked by the hand, and the vessels by thick rubber or glass tubing. E is a screw-clip which can be varied at will. F is a football bladder full of fluid which can be shut off by means of clip G. M is a mercury manometer to measure pressure.

If clip E is open and G closed there is a small pressure during the time the bulb is squeezed, and the flow is intermittent. If E is

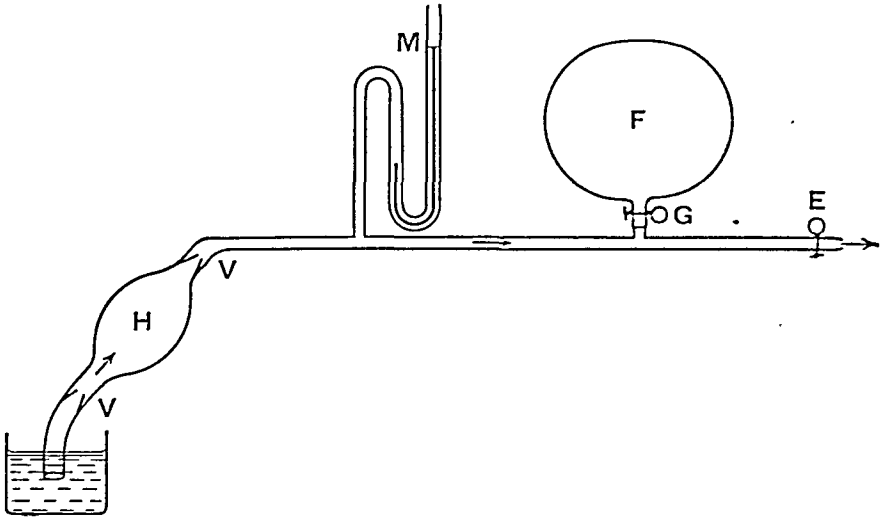


FIG. 65.—Diagram of model to illustrate the parts played by E, peripheral resistance, and F, the elasticity, in maintaining a pressure in the mercury manometer, M. The pump (H) is a bulb syringe with valves, and F is a football bladder.

now tightened the variations in pressure (M) are greater but the flow is still intermittent and greater force is necessary to empty the bulb.

If now the clip G is opened the benefit of adding the elasticity to the system is seen. It becomes easier to empty the bulb, and the fluid which cannot escape past E distends the bag F which recoils during the refilling of H. The fluctuations in pressure are no longer so great and the flow from E is now continuous. By experiment we can show that the tighter E is screwed the higher is the mean pressure. A similar experiment may be made with the familiar war-time stirrup-pump in which the nozzle corresponds to the peripheral resistance and the jet indicates the blood-pressure.

The vessels in the body are not rigid but elastic tubes. When therefore at each beat the left ventricle forces out some 80 c.c. of blood into an already full arterial system the vessels are distended, while when the heart is refilling the vessels recoil to keep up the mean arterial pressure and the flow beyond the arterioles continuous.

In the body the elasticity is not localised to any particular part of the system as in the model, but is generalised. It is supplied by the elastic and muscular tissue in the walls of the vessels themselves.

The resistance corresponding to E of the model is supplied by the arterioles, the relatively thick muscular walls of which are under the control of nerves and in health are kept constantly in a state of partial contraction or tone which may be varied from time to time.

By assisting to maintain the diastolic pressure the elasticity of the system plays an important part in converting the intermittent flow in the arteries into a continuous flow in the capillaries. But for this we might feel the throb of the pulse-beat. If, however, a tissue becomes inflamed its arterioles dilate and the tissues become tense because of congestion with fluid and blood. The throb of the arteries is then transmitted to the nerve-endings. This is why we may feel throbbing in a septic finger or tooth.

The volume of blood pumped out per beat has been discussed fully in relation to the output of the heart. It depends primarily on the extent to which the heart is filled, and this in turn depends on the venous return and on the rate of the heart.

Summary.—We may then summarise by saying that the arterial pressure is maintained by the heart pumping into an elastic system of vessels more blood than can escape during the time of each contraction; the elastic vessels are distended and recoil during the filling of the heart. Thus the arterial pressure is prevented from falling appreciably between the beats, and an intermittent flow produced by the heart is converted into a constant flow in the capillaries.

Recording the Blood-Pressure in Animals.

The fact that the blood exerts considerable pressure on the arterial walls may be readily shown by puncturing any artery; the blood is propelled with great force through the opening, and the jet rises to a considerable height; in a small artery, where the pressure is lower, the jet is not so high as in a large artery: the jerky character of the outflow due to the intermittent action of the heart is also seen. If a vein is similarly injured, the blood is expelled with much less force, and the flow is continuous, not intermittent.

The first to make an advance on this very rough method of demonstrating blood-pressure was the Reverend Stephen Hales, vicar of Teddington (1722). He inserted, using a small brass tube as a cannula, a glass tube at right angles to the femoral artery of a horse, and noted the height to which the blood rose in it. This is a method like that which we used in the first model described (fig. 64). The

blood rose to the height of about 8 feet, and having reached its highest point, it oscillated with the heart-beats, each cardiac systole causing a rise, each diastole a fall. Hales also noted a general rise during each inspiration. The method taught Hales these primary truths in connection with arterial pressure, but it possesses many disadvantages; in the first place, the blood in the glass tube very soon clots, and in the second place, a column of liquid 8 feet high is an inconvenient one to work with.

The first of these disadvantages was overcome to a great extent by Vierordt, who attached a tube filled with saturated solution of sodium carbonate to the artery, and measured the blood-pressure by the height of the column of this saline solution which the blood would support.

The second disadvantage was overcome by Poiseuille, who introduced the heavy liquid, mercury, as the substance on which the blood exerted its pressure; and the U-shaped mercurial manometer was connected to the artery by a tube filled with sodium carbonate solution to delay clotting.

The study of blood-pressure was not, however, satisfactory before the introduction by Carl Ludwig (1847) of the *Kymograph* in which Poiseuille's *hæmodynamometer* was combined with apparatus for obtaining a graphic record of the oscillations of the mercury.

Ludwig, who was Professor of Physiology in Leipzig, is looked upon as the father of the graphic method of making observations which is so much more reliable than visual observation only.

A diagram of the apparatus is given in fig. 66.

An artery is exposed, ligatured at its distal end, and clamped, so that no hæmorrhage occurs; it is then opened, and a glass cannula is inserted and tied in. The form of cannula usually employed (François Franck's) is shown on a larger scale; the narrow part is tied into the artery towards the heart; the cross-piece of the T is united to the manometer; the third limb is provided with a short piece of india-rubber tubing which is kept closed by a clip and only opened when the cannula is being filled at the beginning of the experiment or if the presence of a clot necessitates the washing out of the cannula.

The tube by means of which the cannula is united to the manometer is made of thick rubber, so that none of the arterial force may be wasted in expanding it. The tube, cannula, and proximal limb of the manometer are all filled with a saturated solution of sodium bicarbonate, sodium sulphate, or other salt which will mix with blood and delay its clotting. This is contained in a bottle some feet above the apparatus so that it can be supplied under pressure to the proximal limb of the manometer. Before the clip is removed from the artery, the pressure is raised by opening clip

B so that the mercury rises in the distal limb to a height just greater than that of the anticipated blood-pressure; this prevents blood passing too freely into the cannula when the arterial clip is removed.

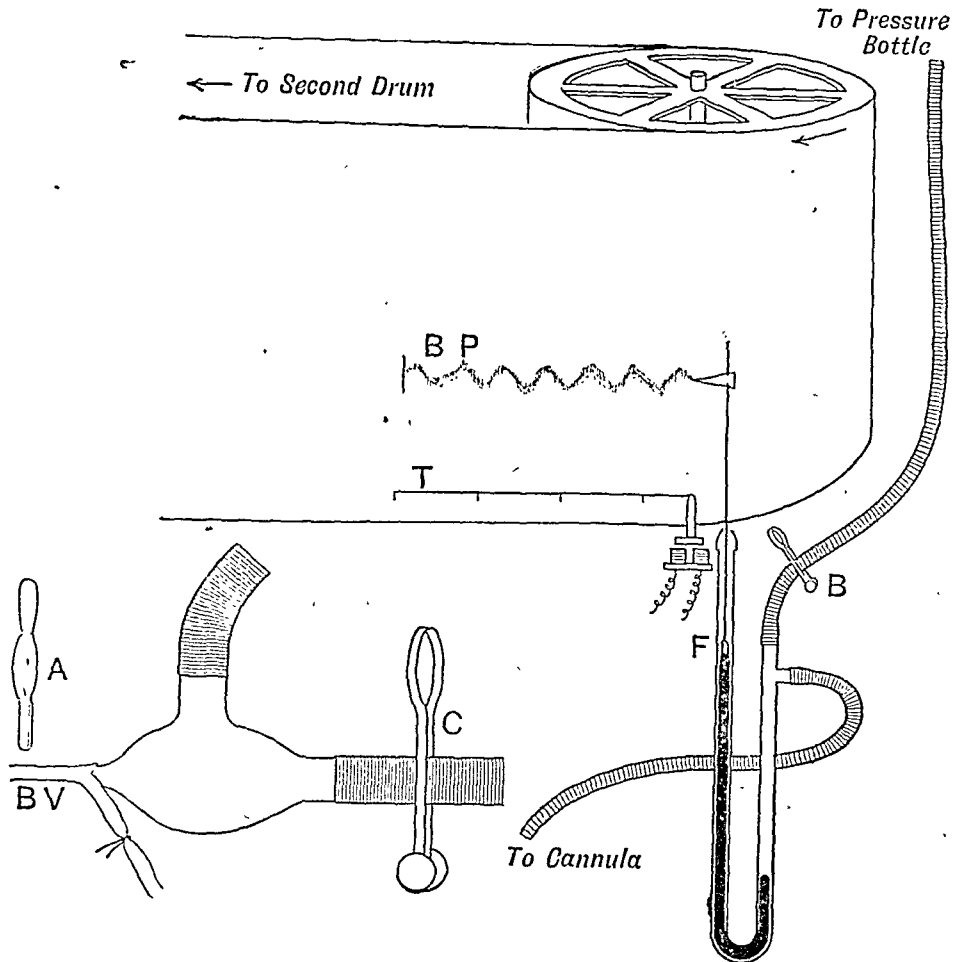


FIG. 66.—The kymograph. A piece of an artery BV is exposed, conveniently the carotid, in the neck, and its peripheral end tied off. A clip, A, is placed on the artery which is then opened and the cannula inserted and tied in. (The ligature is not shown in the figure.) The tubing from the mercury manometer is now connected to the cannula and the tubing filled with fluid under pressure equal to that expected by opening clip B and closing clip C. Clip B is closed and by taking off clip A the artery is put in direct communication with the manometer. BP= blood-pressure tracing. T, electro-magnetic time marker and zero of blood-pressure tracing. F, float of mercury manometer. BV, artery. To wash out the cannula, clip A is applied, and clips B and C opened (McDowall).

In the distal limb of the U-tube, floating on the surface of the mercury, is a float, from which a long wire extends upwards, and carries a stiff piece of parchment which writes on a moving surface covered with smoked paper. When the arterial clip is removed, the writing-point inscribes waves (see figs. 66 and 67), the large waves corresponding to respiration (the rise of pressure in most animals

accompanying inspiration),* the smaller ones to the individual heart-beats. The blood-pressure is really twice as great as that indicated by the height of the tracing above the zero, T, because if the manometer is of equal bore throughout, the mercury falls in one limb the same distance that it rises in the other; the true pressure is measured by the difference of level in the two limbs of the manometer (fig. 66).

It will be observed that the heart-beats indicate that in large arteries there is a considerable fluctuation in pressure between the

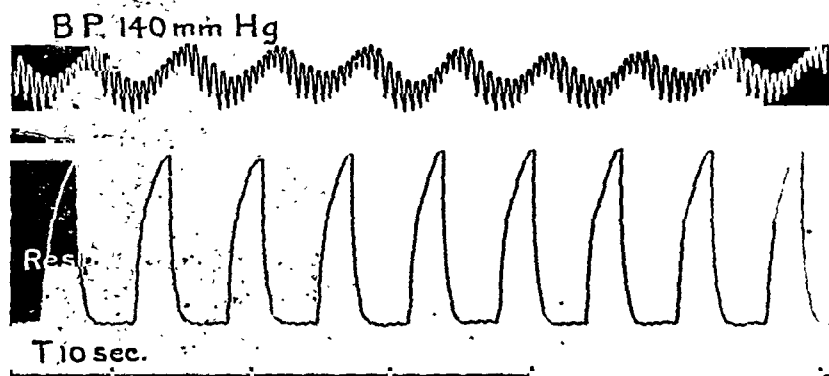


FIG. 67.—Tracing of arterial blood-pressure (B.P.) obtained with a mercurial manometer attached to a cat's carotid. The smaller waves are heart-beats, which are set on larger ones due to the respiratory movements recorded below. The animal was breathing slowly (McDowall).

systole and diastole of the heart. The limits of each are known as the systolic and diastolic pressures respectively. With a mercury manometer, the inertia of the mercury reduces the difference (the pulse pressure), which in man may be as much as 50 mm. Hg. The full extent of the pulse pressure may be recorded by a rapidly moving optical manometer such as that of Piper or Wiggers already referred to on p. 102. The usual method is to construct a scale showing the extent to which the spot of light moves with each 10 mm. Hg rise in pressure.

The measurement of the pressures in the veins and capillaries is dealt with in later sections.

Arterial Blood-Pressure in Man.

A special apparatus known as a **sphygmometer** is used for the measurement of blood-pressure in man. Martin's modification of

* The explanation of the respiratory curves on the tracing is postponed till after we have studied Respiration.

Riva-Rocci's apparatus consists of a four-sided elastic bag about four and a half inches wide, and long enough to encircle the arm. It is wrapped round the arm, and outside it a cuff of strong canvas is firmly strapped. Air is forced into the bag by a tube leading

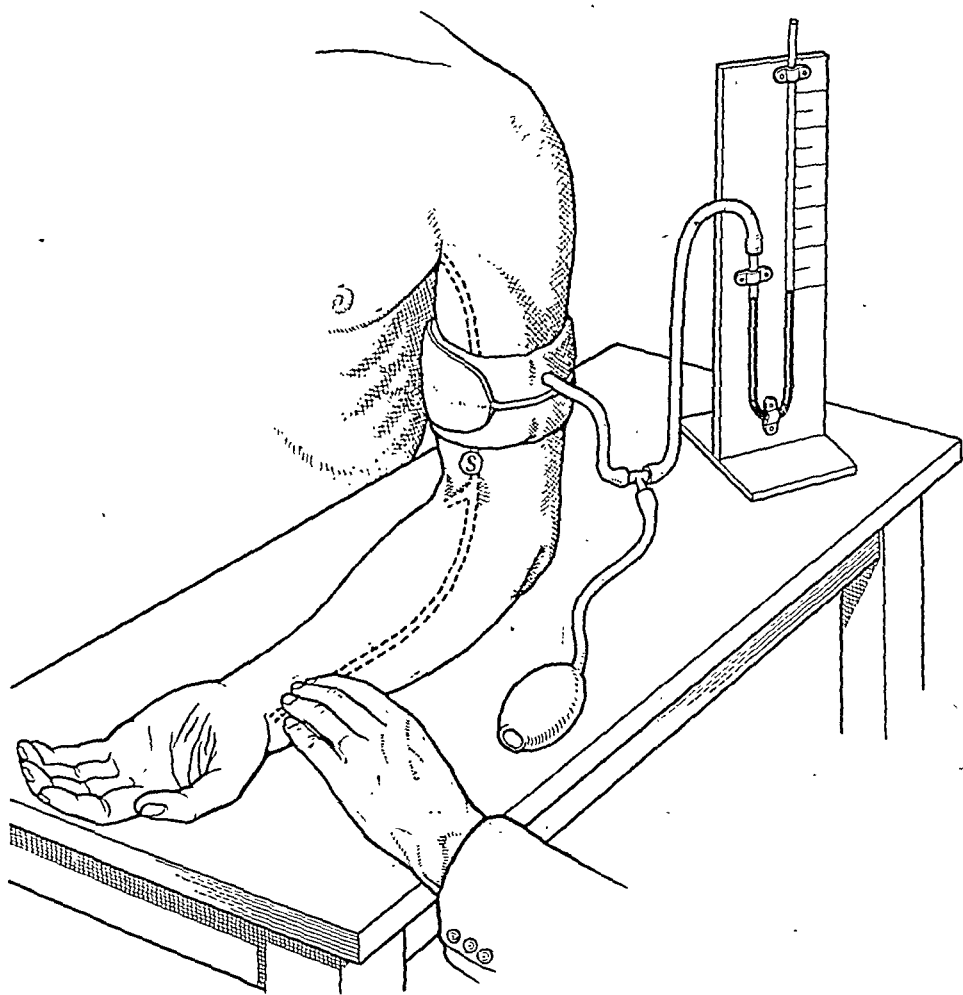


FIG. 68.—The subject's hand is best supported by a table to promote relaxation of muscles. The stethoscope is applied at S. The pressure on the arm-cuff is raised by rhythmically compressing the bulb and is shown on the manometer. It is pointed out that more elaborate varieties of such apparatus have to be calibrated against such a simple U-tube of uniform bore.

from a ball syringe; this tube is also connected by a side branch to a mercury manometer. As one continues to pump and distend the bag, the pulse-beats are transmitted to the mercury which rises in the manometer and oscillates with the pulse-beats. As the pressure rises the oscillations become more pronounced, and at a certain point they exhibit a greater excursion than they do at any

other height; beyond this point of *maximal pulsation*, the oscillations diminish in amplitude, and as the distension of the bag is increased still more, the pressure which is sufficient to obliterate the pulse is at last reached, the oscillations of the mercury cease, and the pulse is no longer to be felt at the wrist. The pressure necessary to do this is equal to the *systolic pressure*, and the height of the mercurial column should be noted when the pulse just disappears. The point of maximal oscillation gives a reading of the *diastolic pressure*.

The *auditory method* introduced by Korotkow has now replaced all other methods for estimating the diastolic pressure and it may be used for systolic also. The armlet is inflated until the compression applied is more than sufficient to obliterate the pulse. The chest-piece of an ordinary binaural stethoscope is applied over the brachial artery just below the armlet. It is advisable also to take the systolic pressure by palpation so as to compare the tactile and auditory indices of pressure. When the armlet is thus distended no sound is heard and no pulse is felt. The air is then allowed to escape gradually from the armlet, and at a certain point, which is read off on the manometer, a distinct sound is heard with each heart-beat. This marks the beginning of the transmission of the pulse through the artery, and is the auditory index of the systolic pressure; it is heard a little earlier than the return of the pulse can be felt at the wrist. With further lowering of the armlet pressure, the sound successively becomes murmurish (second phase); loud and clear (third phase); dulled and weakened (fourth phase); and finally inaudible. The change from the third to the fourth phase, that is, the sudden dulling and weakening of the sound, constitutes the diastolic index. In many instances there is little difference between the dulling and the final extinction of the sound. But often, especially in young adults, the difference may be very marked, amounting sometimes to 30 mm. Hg; to take the abolition of the sound as the diastolic index in such cases would lead to serious error.

In healthy young adults examined by this method in the sitting posture, the *systolic pressure* averages about 110 to 135 mm. Hg and the *diastolic pressure* between 60 and 80 mm. in different individuals. Muscular exertion and mental excitement raise the pressure, especially the systolic (see p. 169). The difference between systolic and diastolic pressure is termed the *pulse-pressure*. In disease there are great variations, and the study of these is a very valuable aid to diagnosis.

There is on the market a large variety of manometers, some containing mercury and some on the aneroid principle which magnify the changes which occur about the range usually found, i.e. 90 to 200, but it is necessary to calibrate the latter manometers

from time to time against the simple and much cheaper U-tube of mercury which, however, has the disadvantage that it is less portable because of the danger of spilling the mercury in transit.

The following table gives the average height of blood-pressure in various parts of the vascular system in man. They have been very largely inferred from experiments on animals, but in many cases have been confirmed by experiments on man:—

Large arteries (<i>e.g.</i> carotid)	.	140 mm. (about 6 inches) mercury.
Medium arteries (<i>e.g.</i> radial)	.	110 mm. mercury.
Capillaries (arterial end)	. . . 30 to 35	" "
Capillaries (venous end)	. . . 15 to 20	" "
Small veins of arm	. . . 9	" "
Portal vein	. . . 10	" "
Inferior vena cava	. . . 3	" "
Large veins of neck	. . . from 0 to - 8	" "

The pressure in the pulmonary artery is about a quarter of that in the systemic arteries. It cannot be recorded in man, but in animals it may be taken by putting a cannula in a branch of the pulmonary artery.

The blood-pressure falls slowly in the great arteries and manifests oscillations corresponding with the alternate systole and diastole of the heart; at the end of the arterial system it falls suddenly and extensively in

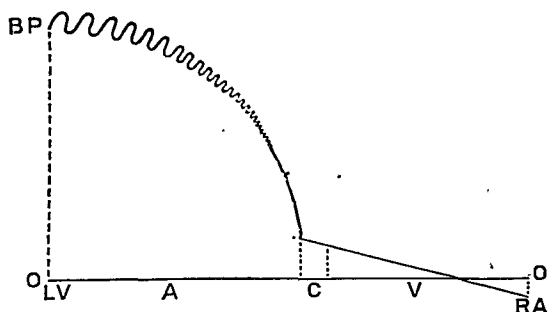


FIG. 69.—Height of blood-pressure (BP) in LV, left ventricle. A, arteries; C, capillaries; V, veins; RA, right atrium; O, line of no pressure.

the course of the arterioles; it again falls gradually through the capillaries and veins. Such a diagram of blood-pressure is thus very different from one of velocity; the velocity like the pressure falls from the arteries to the capillaries, but unlike it, rises again in the veins.

Fig. 69 represents roughly the fall of pressure along the systemic vascular system.

It indicates that the chief peripheral resistance is in the small arteries; this is probably true when the tissue is active and when the capillaries are all open, but the work of Dale and Richards indicates that in some circumstances the capillaries play a larger part than the diagram indicates. (See fig. 75.)

It must be understood that these pressures are subject to considerable variations from alteration of the variable factors on which blood-pressure depends.

The Pulse.

This is the most characteristic feature of the arterial flow. It is the response of the arterial wall to the changes in lateral pressure caused by the heart-beat.

The physician usually feels the pulse in the radial artery, since this is near the surface, and supported by bone. It is a most valuable indication of the condition of the patient's heart and vessels. It is necessary in feeling a pulse to note the following points:—

1. *Its frequency*: this gives usually the rate of the heart but strictly only the number of beats of the left ventricle which produce pulse-waves strong enough to reach the wrist.
2. *Its force*: whether it is a strong, bounding pulse, or a feeble beat; this indicates the force with which the heart is beating.
3. *Its regularity or irregularity*: irregularity may occur owing to irregular cardiac action either in force or in rhythm.
4. *Its tension*: that is, the force necessary to obliterate it. This gives an indication of the height of the blood-pressure.
5. The condition of the arterial wall which in disease may become thickened.

In order to study the pulse more fully, it is necessary to obtain a graphic record of the pulse-beat, and this is accomplished by the use of the **sphygmograph**. It is not an easy instrument to use on all subjects and its use has been discontinued clinically because it gives little more information than can be obtained from feeling the pulse and taking the blood-pressure. It is best studied practically.

Fig. 70 represents a typical sphygmographic tracing obtained from the radial artery.



FIG. 70.—Diagram of pulse-tracing. A, up-stroke; B, down-stroke; C, pre-dicrotic wave; D, dicrotic; E, post-dicrotic wave.

The main waves recorded are the *primary* (A) wave which is due to ventricular systole expanding the artery and the *dicrotic wave* (D). The dip before the wave is commonly called the *dicrotic notch*.

The primary cause of the dicrotic wave is the closure of the aortic valve; as already explained when we were considering the cardiac valves, the outflow of blood from the heart suddenly ceases, and the blood is driven back against the closed aortic valve by the elastic recoil of

the aorta; the wave rebounds from this and is propagated through the arterial system as the dicrotic elevation. The production of the dicrotic wave is favoured by a low blood-pressure when the heart is beating forcibly, as in fever. Such a pulse is called a dicrotic pulse (fig. 71), and the second beat can easily be felt by the finger.

Other subsidiary waves may occur, notably an anacrotic wave on the upstroke, which results from a high peripheral resistance which tends also to prolong the downstroke.

If a long pulse-tracing is taken, the effect of the respiration may be seen in an increase of pressure, and, in some people, a slight acceleration of the heart's beats during inspiration.

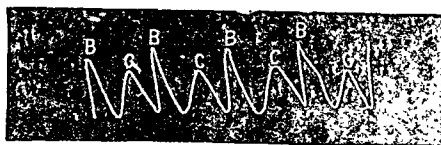


FIG. 71.—Dicrotic pulse.

The main waves of the pulse can be demonstrated without the use of any instrument at all, by allowing the blood to spurt from a cut artery on to the surface of a large sheet of white paper travelling past it. We thus obtain what is called a *haemautograph* (fig. 72).

The pulse-wave travels along the arteries, and is started by the propulsion of the contents of the left ventricle into the already full arterial system. The more distant the artery from the heart, the longer the interval that elapses between the ventricular beat and the arrival of the pulse-wave. Thus it is felt in the carotid earlier than in the radial artery, and still later in the dorsal artery of the foot. The difference of time is, however, very slight; it is only a small fraction of a second.



FIG. 72.—Hæmauto-graph, to be read from right to left.




FIG. 72.—Hæmauto-graph, to be read from right to left.

The rate of propagation of the pulse-wave is of some importance since for a given blood-pressure it indicates the elasticity of the arterial wall. It travels at the rate of from 5 to 10 metres per second, that is twice or thrice the velocity of the blood-flow. The method of ascertaining this may be illustrated by the use of a long elastic tube into which fluid is forced by the sudden stroke of a pump. If a series of levers are placed along the tube at measured distances, those nearest the pump will rise first, those farthest from it last. If these are arranged to write on a revolving cylinder under one another, the movements will be shown graphically, and the time-interval between them can be measured by a time-tracing. The same principle is applied to the arteries of the body; a series of Marey's tambours is applied to the heart and to various arteries at known distances from the heart; their levers are

arranged to write immediately under one another. The difference in time between the commencement of their up-strokes is measured by a time-tracing.

A. V. Hill has introduced the hot-wire sphygmograph in which the expansion of the artery with each heart-beat makes a puff of air cool an electrically-heated wire, the electrical resistance of which is thereby varied. The wire forming one arm of a Wheatstone's bridge, the alteration in resistance is shown by a string galvanometer, and recorded photographically. Two arteries at different distances from the heart are used, the time of arrival of the pulse-wave in each being recorded by the excursion of a string in the galvanometer: the two strings being arranged so that their images on the recording surface fall in the same vertical plane. Wishart has introduced another sphygmograph in which the pulse is caused to move the plates of a condenser. All such methods are more accurate than that of the tambour but require more expensive apparatus.

The Venous Pulse and the Polygraph.

The venous pulse is recorded by placing over the lower end of the internal jugular vein in the neck a hollow metal cup which transmits changes in pressure to a delicate tambour. The waves are produced in part by interruption of the venous inflow and by the neighbouring arteries. Thus when the auricle is filling, the venous pressure rises to cause the V wave (fig. 73), but this falls as soon as the auriculo-ventricular valves open. The subsequent filling and contraction of the auricle cause the important A wave, which is followed $\frac{1}{2}$ of a second later by the C wave. This wave is due to the approximation of the large arteries and veins, *e.g.* the innominate, and, since the wave is present in pressure records of the auricle itself, it may in part be due to the bulging of the floor of the auricle during ventricular systole.

An analysis is made of the venous tracing by taking simultaneously a tracing of the radial pulse by means of the **polygraph** in which the venous and arterial records are on the same strip of paper (fig. 73). The wave which occurs on the venous tracing **one-tenth of a second** before the radial pulse is the C wave, while usually the preceding wave is the A wave. Fig. 73 shows additional waves which can be neglected at present.

The importance of polygraph records is that from them the number of auricular contractions may be counted and the *a-c* interval, which corresponds to the P.R. interval of the electro-cardiogram, gives a measure of the time (**normally one-fifth of a second**) taken for the excitation wave to pass down the auriculo-ventricular bundle.

The Time of a Complete Circulation.

The simplest method of making this estimation is that of Stewart. A solution of methylene-blue is injected into a vessel. The corresponding vessel on the opposite side is exposed, placed

on a sheet of white paper, and strongly illuminated. The time is noted between the injection and the moment when the blue colour is seen to appear in the vessel under observation. Stewart applied this method also for determining the time occupied by the passage of blood through various parts of the circulation; the

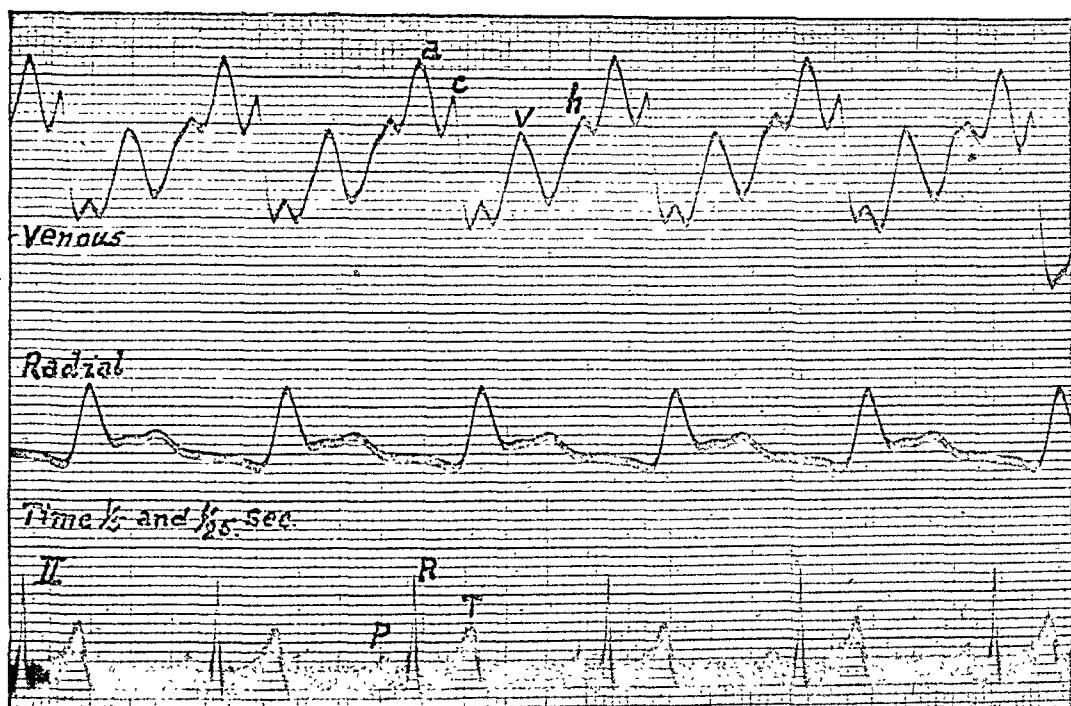


FIG. 78.—Simultaneous electro-cardiograph (lowest) and polygraph (upper two) records.
(From Flint's *The Heart: Old Views and New.*)

longest circulation times were found in the portal system and the lower limbs. He calculated that the total circulation time in man is about 15 seconds.

None of these methods, however, give the true time of the entire circulation; they give merely the shortest possible time in which any particle of blood can travel through the shortest pathway. The blood that travels in the axial current, or which takes a broad pathway through wide capillaries, will arrive far more speedily at its destination than that which creeps through tortuous or constricted vessels. Since the total blood in the body and the output of the heart per minute are about the same, *i.e.* 5 litres, it can be considered that all the blood makes one circuit per minute—at rest. During exercise the rate is greatly increased. The blood passing through regions near the heart, *e.g.* through the coronary circulation, performs the journey most rapidly. Such considerations reduce the average time to something like that calculated by Stewart.

The Capillary Circulation.

It used to be thought that the capillaries simply opened up when the blood-pressure rose, but since the work of Krogh it has become appreciated that they have a power of contraction and dilatation quite independent of the arteries, and are even able to close against a raised blood-pressure.

We have already noted (p. 94) that capillaries close because of a swelling of the endothelial cells of which their walls are composed. The blood-pressure varies in different capillaries. It is most accurately measured by inserting a minute cannula into the vessel under a microscope, but a rough idea is obtained by finding the amount of pressure necessary to close the vessels or blanch the skin by sealing over it a glass capsule into which air may be forced.

It is evident that the capillary pressure is much lower than that in the arteries.

In the human skin at heart level the pressure has been found to fall because of the resistance to the blood flow, from 32 mm. of mercury at the arterial end to about 12 mm. at the venous end, but in some capillaries, *e.g.* those of the foot in the erect posture, the pressure is much higher.

The circulation in the capillaries may readily be observed in the web of the foot, or the mesentery of a frog. In the larger vessels there is seen to be a distinct pulsation with each heart-beat, but in the smaller capillaries the blood is seen to flow with a constant equable motion. The red blood corpuscles move along mostly in single file and bend in various ways to accommodate themselves to the tortuous course of the capillary, but they recover their normal outline on reaching a wider vessel. If the capillaries are observed for some time they are seen to undergo changes in calibre, some shutting down, and others opening up. These changes apparently take place independently of the arteries and veins, and depend on the oxygen requirements of the tissue supplied.

The capillaries may readily be made to contract if touched with a sharp needle. This contraction normally spreads over a considerable area, but if cocaine has been previously applied to the web, the constriction is limited to the point of stimulation. Since cocaine is a known paralyzant of nervous tissue this experiment indicates that the capillaries are controlled by nerves. This is supported by the observation of Hooker that stimulation of the cervical sympathetic nerves causes constriction of the capillaries of the rabbit's ear, while Doi has demonstrated dilatation in the frog's web by nervous stimulation (Bayliss).

It will be noted that the capillaries being very thin-walled are easily affected by substances acting on them from the outside.

In relation to exercise in a subsequent section we shall see that the capillaries dilate in all active tissues. We are then not surprised to find that substances normally released or produced during tissue activity, such as carbon dioxide and lactic acid, cause capillary dilatation. This no doubt accounts for the fact that we readily obtain flushing of the skin after compressing a small area

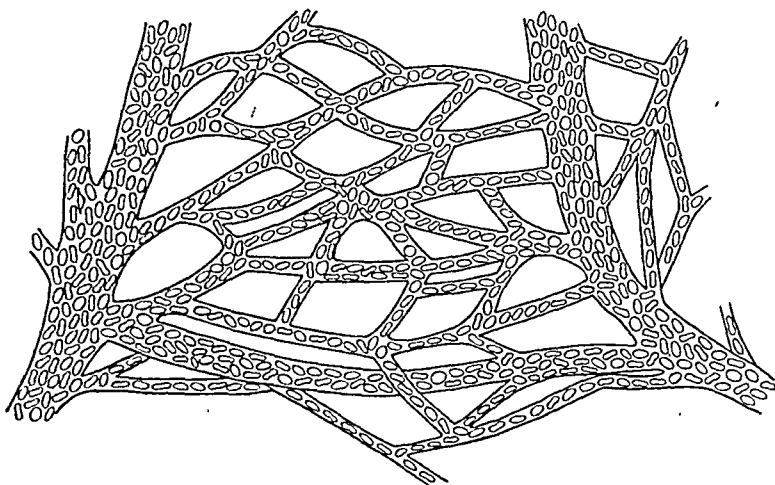


FIG. 74.—A capillary circulation showing an arterio-venous anastomosis in its lower part.

or after temporary occlusion of the blood-supply (see Exercise). The fact that there actually is a dilatation of vessels during the occlusion has been definitely shown by the fact that the venous pressure in the occluded part falls (Kendrew). Recent work suggests that adenine triphosphate may be released from muscle cells and be largely responsible for the dilatation (Fleisch).

The human capillaries may be observed in the skin with an ordinary microscope, if the skin is soaked in oil and adequately illuminated. In the nail-fold capillary loops may be seen. Some skin capillaries remain permanently open but others open and close at intervals.

The Capillaries and Circulatory Capacity.

It is important to realise that the total number of the capillaries in the body is enormous, and that were they all open at once the effect on the capacity of the vascular system would be very great. They would, as it were, soak up the blood like a sponge.

The following figure gives an idea of the variable capacity of the circulation. When, therefore, the arterioles and the capillaries as a whole dilate, there may be a momentary increased flow into the veins but the total effect is a reduction of the venous flow.

The student at this stage should realise that the capillaries may cause changes in the blood-pressure in two ways, (1) by varying the capacity of the circulation or (2) by varying the peripheral resistance if the arterioles are dilated at the same time.

It has been shown (Dale and Richards) that the substance **histamine** has the power of causing widespread capillary dilatation,

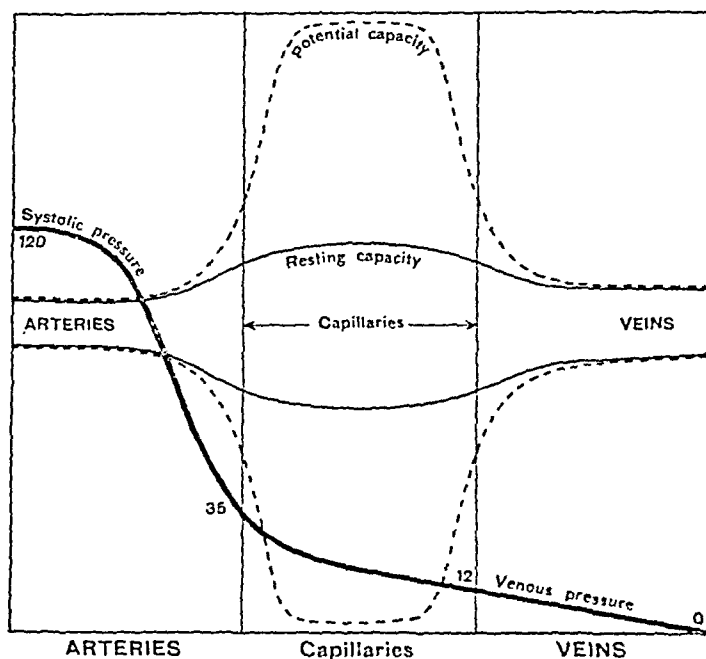


FIG. 75.—Diagram indicating the potential capacity of the circulation at its different points. The corresponding resistance is indicated approximately by the blood-pressures in the various regions.

and brings about, as a result, a profound fall of blood-pressure, which may end in death. The blood is lost in the capillaries and does not return to the heart. Death from superficial burning is probably due to the production of such a substance in the damaged tissues, since the symptoms of this condition are likewise explained by a diminution of the blood in active circulation.

A network of capillaries containing corpuscles, some of which go in single file, is seen in fig. 74. At one side (right) is seen an arteriole, at the other a venule. Near the bottom of the figure is seen an arterio-venous anastomosis.

The capillaries of the skin have been found to be specially sensitive to histamine, an observation possibly explained by the finding of Best, that the skin, unlike the other tissues of the body, does not contain the enzyme histaminase which destroys histamine. Lewis has shown that when the skin is injured the redness and whealing (*e.g.* in burns) is due to the local production of a dilator

substance which not only opens up the capillaries but causes increased permeability of their walls. This is evidently a protective mechanism.

Fainting in a hot bath is probably also due to a dilatation of the capillaries of the skin.

Considerable discussion has taken place on what normally keeps a large number of the capillaries closed. It is probably nervous control, but the closure returns after the nerves are cut. It appears likely that the capillaries, like cardiac muscle, become responsive to the chemical constituents of the blood, for it has been found that perfused vessels are exquisitely sensitive to minute changes in the concentration of substances normally present in the blood, especially to the calcium-potassium and to the acid-base ratios.

The Venous Pressure and Return.

In our study of the output of the heart we saw that this depends primarily on the amount of blood which reaches it from the veins. This return depends on a variety of factors, and provided the heart is efficient its extent may be estimated by recording the venous pressure.

The Venous Pressure.—This pressure is clearly dependent on the heart and the arterial pressure. The pressure is highest in the small veins at the periphery, but falls off to zero or a minus pressure in the veins near the heart during diastole. The pressure in veins may be taken exactly as is arterial pressure, except that since the pressure is so low, water is used in the manometer instead of mercury. An inverted bell of very thin glass makes a convenient float. In animal experiments sodium bicarbonate is the usual fluid used in the manometer as it is an anti-coagulant, and also no serious harm results if some gets into the circulation. The best way to obtain a record is to insert a long cannula down the external jugular vein. A good venous pressure record shows respiratory waves and heart beats. In man, probably the most trustworthy way is to observe the pressure at which a saline solution will just stop running into a vein through a cannula. The amount of pressure necessary to compress a superficial vein or which will just prevent the re-filling of a vein emptied by compression from the periphery inwards is also an index of the venous pressure. The venous pressure is normally about 5 to 15 cm. H_2O or about 3 to 10 mm. Hg in a vein at the elbow, held at the level of the right auricle (Bedford and Wright).

The venous pressure varies directly with the blood volume relative to the capacity of the circulation; in this way it is

different from the arterial pressure, which may be kept up reflexly by the vasomotor centre. If blood is lost, the arteries and capillaries constrict and by increasing the peripheral resistance keep up the arterial pressure, but as a result (corresponding to a closing of the tap in fig. 64) the venous pressure falls. This adaptation also occurs whenever a drug is injected which causes any marked increase in the capacity of the circulation. It is seen after the injection of histamine (see Capillaries, p. 143) and of alcohol, which dilates skin vessels, although in neither instance may there be, at least with small doses, any sustained fall of arterial pressure.

When, however, there is a large increase in the capacity of the circulation, as when a large dose of histamine is injected (*e.g.* 2 mg. histamine into a cat), or when the nervous control of the blood-vessels is cut off, then there is a fall of venous pressure and failure of the circulation because the heart does not receive sufficient blood. This phenomenon occurs whenever there is generalised asphyxia of the body and is produced by a variety of causes, but especially a low blood-pressure which fails to distribute the blood properly. This condition of **shock** which is sometimes fatal is of great surgical importance in cases of injury, but its treatment is most baffling since not only is there an increased capacity of the circulation, but also a reduced peripheral resistance. So far as is known this state is irreversible once established and every effort must be made to prevent it.

The venous pressure is also much influenced by the efficiency of the heart as a pump, and the weaker the heart becomes the greater is the venous pressure because blood continues to flow into the veins from the arteries, the blood in which is at a much higher pressure (see fig. 79). There is, indeed, evidence that the height of the venous pressure is the most delicate test of the efficiency of the heart. A rise of venous pressure is very commonly seen in cardiac diseases, and the venous congestion so produced may cause dire results.

On the other hand, increased efficiency of the heart causes a fall of venous pressure.

When for any reason the venous pressure becomes high, the capillary pressure is increased and the flow through the capillaries delayed. Lack of oxygen leads to increased capillary permeability and this combined with increased capillary pressure results in the passage of excess fluid into the tissues. Such an excess is called *oedema* or *dropsy*. A mild degree of this occurs in the lower limbs from standing still for twenty minutes.

The return of blood to the heart is essentially brought about by the arterial pressure. In most animals the heart is as emphasised by Franklin at almost the lowest point of the circulation. The return

is therefore facilitated by gravity with the exception of the blood from the limbs where the valves assist.

In exercise the return of blood is facilitated by the muscular contractions, which compress the capillaries in the muscle itself and also to some extent the valved veins. The dilatation of the capillaries permits a more rapid flow of blood from the arteries to the veins.

The return of the blood to the heart is still further assisted by respiration. Indeed, so important is this function that the term "*respiratory pump*" is used (L. Hill). Any temporary cessation in respiration causes a fall in arterial blood-pressure, until asphyxia ensues. The pressure in the chest is normally negative. During each inspiration there is produced an increased negative pressure in the chest and at the same time an increased positive pressure in the abdomen. The negative pressure in the chest tends to draw blood into it, and the positive pressure in the abdomen to drive up blood. Thus at each inspiration, since the valves of the veins prevent regurgitation into the lower limbs, blood is drawn towards the heart while that in the lungs is trapped by the pulmonary valves. During expiration, therefore, it is forced towards the left side of the heart (see "The Effects of the Respiratory Movements on the Circulation" later). The action of the respiratory pump is increased with the respiration during exercise.

CHAPTER XIV

THE CONTROL OF THE CIRCULATION.

THE circulation is controlled by chemical and nervous mechanisms which maintain its efficiency in whatever circumstances the body may be placed. One great purpose of the control is to provide wide variations in blood supply to various organs, especially the muscles according to their activity and requirements. The control also prevents the efficiency of the circulation from being unduly affected by changes in the position of the body and ensures that in the event of loss of blood, the heart and brain—the most essential organs of the body—are the last to suffer seriously.

THE FUNCTION OF CARDIAC CONTROL.

The control of the heart confers on the organ the power of changing its output and adapting it to the needs of the animal. This it does, as we have seen, by changing its output per beat and the number of beats per minute. It is in regard to the latter that the nervous control of the heart is of special importance, but the nervous control also makes the response of the cardiac muscle more effective.

The Control of the Heart-Rate.—This rate is set by the pace-maker, which may be influenced appreciably by various factors, especially those which reach it by way of the sympathetic and the vagus nerves. In addition, the rate is affected by the temperature of the blood reaching the pace-maker, and by the amounts of thyroid and adrenal hormone circulating in the blood. Normally these are of little significance but they become important in disease.

THE NERVOUS CONTROL

The Sympathetic.—In the mammal the sympathetic fibres leave the cord by the anterior roots of the second to the sixth dorsal nerves (Cannon, see fig. 39); they pass by the rami communicantes to the stellate ganglion, or first thoracic ganglion, and thence by the annulus and by the inferior cervical ganglion of the sympathetic they proceed to the heart (see fig. 76).

In man, the cardiac branches of the sympathetic travel to the heart from the annulus and cervical sympathetic in superior, middle

and lower bundles of fibres. These pass into the cardiac plexuses, and surrounding the coronary vessels ultimately reach the heart.

In the frog the sympathetic fibres leave the spinal cord by the anterior root of the third spinal nerve, and pass by the ramus communicans to the third sympathetic ganglion, then to the second

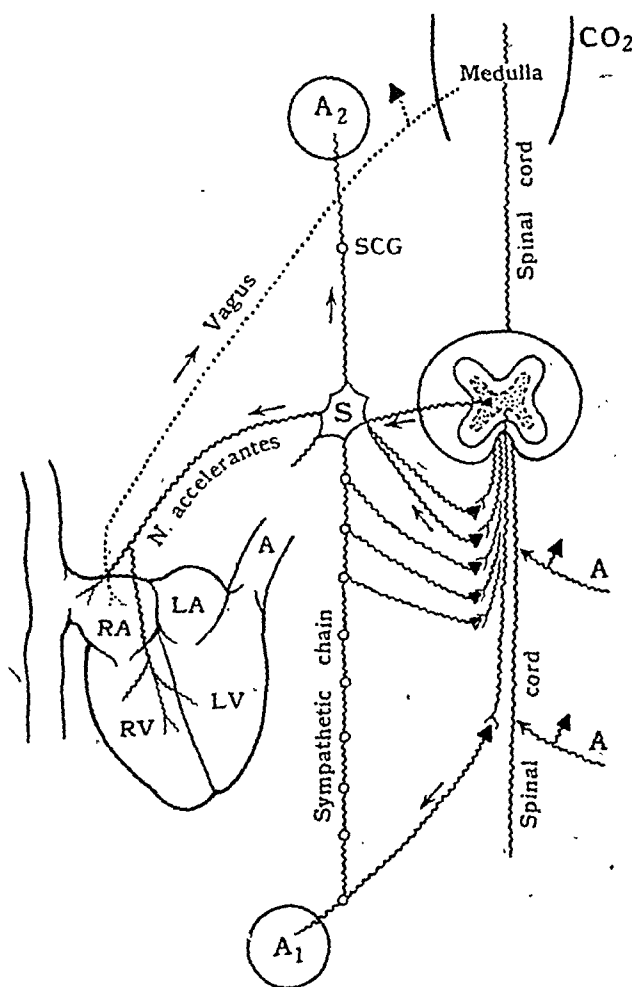


FIG. 76.—Diagram to show the chief pathways concerned in sympathetic acceleration of the mammalian heart. The known afferent impulses pass upwards by the vagus and from the skin, A. A₁ and A₂, vessels supplied. SCG, superior cervical ganglion. S, stellate ganglion.

sympathetic ganglion, then by the annulus round the subclavian artery to the first sympathetic ganglion, and finally in the main trunk of the sympathetic, to near the exit of the vagus from the cranium. Here they join the vagus and run down to the heart within its sheath, forming the joint vago-sympathetic trunk. The fibres of the sympathetic which go up into the skull are for the

supply of blood-vessels there. It should be noted that the frog has no accessory nerve.

The sympathetic fibres appear to pass to Bidder's ganglion at the junction of the auricles and the ventricle. This ganglion acts as a relay station.

The fibres from the brain appear to pass down the spinal cord

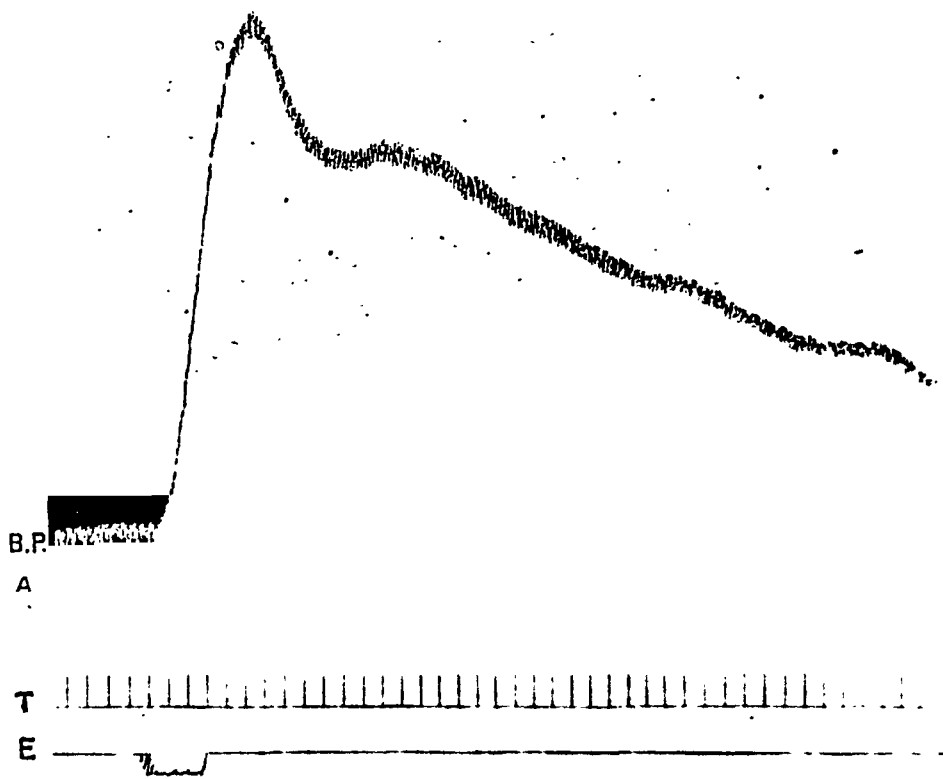


FIG. 77.—Rise in arterial blood-pressure produced by stimulating the central end of a sensory nerve (external popliteal) in a cat under the influence of morphine and curare. B.P., blood-pressure; A, abscissa or base-line; T, time intervals of 5 seconds; E, signal line, the lowering of which indicates the period of stimulation of the nerve. The size of the figure is slightly reduced in reproduction. (Sherrington.)

in its lateral columns, but detailed information on their origin is lacking.

Stimulation of the fibres anywhere along their course brings about cardiac acceleration and augmentation. There is, however, evidence that separate fibres may be concerned in these two functions, and it is claimed that in mammals one or two small nerves leaving the stellate ganglion produce augmentation without acceleration.

The upper end of the sympathetic has not been accurately defined although the term cardiac-accelerator centre is commonly

This source of stimuli appears to be important in exercise when the auricular pressure rises. The exact source of the sympathetic drive which is present at rest is unknown, but the above facts suggest that it, the sympathetic, is constantly receiving impulses from all parts of the body and especially from the external environment. Sympathetic activity is increased in exercise, in anæmia,

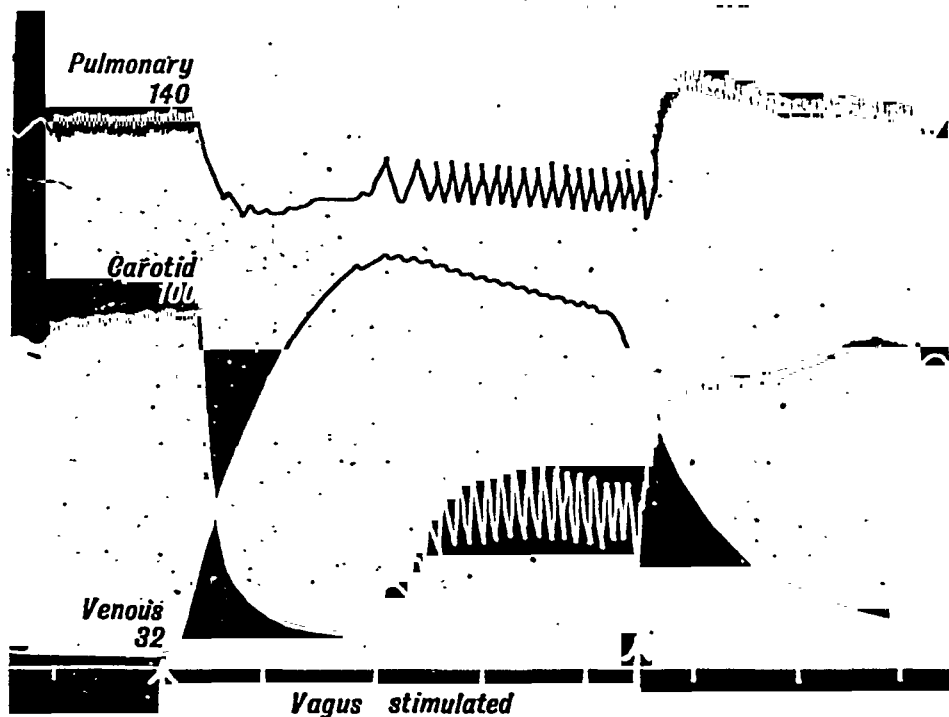


FIG. 79.—Shows the effect of stimulating the vagi on the arterial (pulmonary and carotid) and venous pressures taken simultaneously. Note that although stimulation was continued, an escape occurred, which in this instance was confined to the ventricles. The venous and pulmonary pressures were recorded by water manometers and the pressures are shown in mm. H_2O , that of the carotid in mm. Hg. (McDowall)

in asphyxia, and by a fall of arterial blood-pressure. In exercise the increased action is brought about by the increased mental activity and the rise of blood-pressure in the right auricle.

Sympathetic activity is normally held in check by those reflexes which increase vagus activity.

Increased activity of the sympathetic by increasing the output of the heart causes a *rise in blood-pressure* which, as we shall see, is usually, in the intact animal, further enhanced by constriction of the blood-vessels which is produced at the same time by the excitatory agent, *e.g.* sensory stimulation (fig. 77).

The Vagus.—The vagus is the tenth cranial nerve and is

the chief nerve of the parasympathetic or cranio-sacral division of the autonomic nervous system. Stimulation of the vagus brings about a marked slowing or cessation of the activity of the heart, in the first instance complete, causing a marked fall of arterial and rise of venous pressure. If the stimulation is continued, so-called vagus escape (or escape from the inhibitory stimulus) may occur as the result of the rise of venous pressure stimulating the cardio-accelerator mechanism. This is shown by the fact that if steps are taken to prevent the rise of venous pressure *e.g.* by bleeding, vagus stimulation

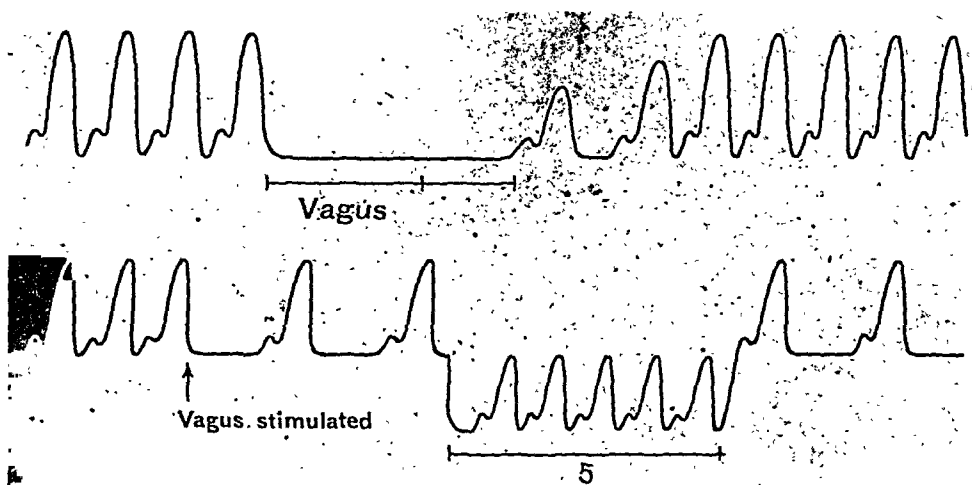


FIG. 80.—The effect of stimulation of the vagus in the frog. Note the slow recovery of the heart in the upper record. In the lower record the vagus was stimulated from the arrow but during 5 additional tension was put on the lever.

continues to cause slowing for hours without evidence of fatigue (McDowall).

In the frog a similar inhibition is produced, but since in the latter the sympathetic is bound up with the vagus mixed effects may occur (fig. 80). It is important to observe that if records of the frog's heart are being taken with the usual form of cardiograph, any form of mechanical stimulation, such as a too-heavy lever; may diminish or annul the vagus effect. So also will too strong a stimulus which may stimulate the heart-fibres directly.

In the frog the inhibitory fibres have a relay station in Remak's ganglion in the sino-auricular junction. The synapses in the junction may be paralysed by painting the region with nicotine but thereafter the heart may still be slowed by stimulating the post-ganglionic fibres which arise in this region which is recognisable as a white line or crescent. If, however, the heart is now painted with atropine no inhibitory effects can be produced (see pp. 85 and 156).

The chief action of the vagus in the mammal is on the sino-auricular node, and on the auricle, of which the force of contraction is reduced, the duration of systole lengthened, and the refractory period diminished. The vagus also depresses the conductivity of the auriculo-ventricular bundle. This is shown by the fact that if a partial heart-block is produced, stimulation of the vagus may make it complete.

It is now known that the vagus acts by liberating a chemical substance, acetyl-choline, in the heart (Loewi). This substance had long been known to have a similar action to that of the vagus. Howell had previously suggested that the action was due to the liberation of potassium, and it may be that somehow his findings are related to those of Loewi, which have already been described on p. 65.

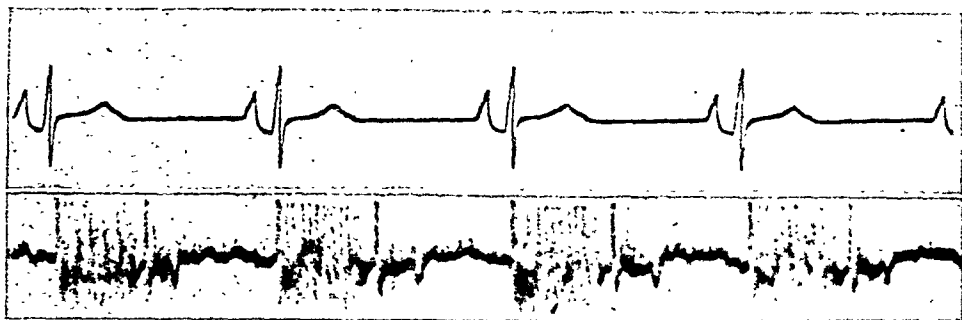


FIG. S1.—A record of the currents of action in the depressor nerve of the cat. From the electrocardiogram above it is seen that there is a burst of impulses during the systole of the ventricles (Greenwood and McDowall).

The Cardio-Inhibitory Reflexes.—During rest the vagi are constantly sending out impulses to restrain cardiac activity as is indicated by the fact that if they are cut, or if their action is prevented by atropine, there is cardiac acceleration. Moreover, it can be shown that this vagus restraint depends on the receipt by the vagus centre of afferent impulses, the loss of which leads to cardiac acceleration. These impulses arise in the walls of certain blood-vessels during each systole of the heart.

In 1865 Cyon had discovered that there runs with the vagus a nerve known as the aortic depressor,* stimulation of the central end of which causes a fall of blood-pressure and slowing of the heart by way of the vagus. Now it has been shown that at each beat of the heart impulses pass up this nerve to the medulla (Adrian and Bronk, Rijlant). (See fig. S1.)

The impulses arise as a result of the stretching of the walls of the aorta and the left side of the heart. This has been finally

* This is a separate nerve in the rabbit, but in most mammals it is bound up with the vagus. In the cat it is sometimes separate.

shown by Daly and Verney, who short-circuited the arch and obtained cardiac slowing by stretching it.

Even between the beats there may be a considerable upward discharge of impulses in the depressor if the aortic pressure is caused to rise by the intravenous injection of fluid or of adrenaline.

In 1925 Hering discovered that similar distension of the region known as the carotid sinus at the bifurcation of the common carotid artery had a like effect and this has been fully confirmed and studied, especially by Heymans. It is possible to separate the carotid sinus from the circulation with its nervous connections intact and to supply it with blood at different pressures. It has been shown that impulses pass to the medulla by way of a branch of the glossopharyngeal nerve. Thus we may say that the normal vagus activity is maintained reflexly from the cardio-aortic region and the carotid sinus.

These two reflexes are responsible for the observations of Marey that the higher the blood-pressure the slower the heart and *vice versa*. The vagus centres may also be stimulated by a number of other procedures, such as a blow on the abdomen or larynx, but it is doubtful if they have any physiological significance except that they show reflex paths.

An increase in cerebral pressure also brings about similar results, apparently through direct action on the medulla. The cardiac slowing produced is an important sign of bleeding into the cranial cavity in cases of fractured skull.

The Relation of the Sympathetic to the Vagus.—The sympathetic and vagus are not so antagonistic as at first sight appears, rather they assist each other in providing the heart with a wide range of activity, for when the heart is accelerated normally or by sensory stimulation there is a reduction of the normal vagus restraint. This was shown by Gasser and Meek and by Heymans and Samaan, who compared the effects of exercise on animals before and after cutting the sympathetic and vagus.

It has indeed been shown that the reduction of vagus restraint is certainly as important as increased sympathetic action. How exactly the changes are brought about is not certain, but it is clear that psychical effects and the effects of afferent impulses play an important part.

It has, however, been suggested that the cardio-inhibitory reflex has an important function in relation to cardiac efficiency. The more efficient the heart the more blood it is capable of pumping out per beat, but the cardiac acceleration which takes place when the venous pressure rises in exercise would prevent full advantage being taken of the increased efficiency unless vagus restraint during rest were increased. This function would explain why those in good

training develop increased vagus restraint. It would seem then that the essential function of the cardio-inhibitory mechanism is to increase the range of the heart-beat by extending its lower limit.

It is also believed that by such reflexes the heart is protected against a sudden rise of pressure on the arterial side. If such a rise is produced, it is at once reduced by cardiac slowing and vascular dilatation.

The Chemical Control of the Heart-Rate.

Any procedure which causes oxygen-want and the accumulation of carbon dioxide in the brain causes cardiac acceleration which at a later stage is replaced by cardiac slowing. Since the acceleration occurs even after the vagi are cut, the sinuses denervated, and the suprarenal glands removed, it must be considered that such procedures cause a central stimulation of the sympathetic (McDowall). At the same time they cause apparently an inhibition of the cardio-inhibitory reflex since, under conditions of oxygen-want and carbon dioxide accumulation in exercise and asphyxia, cardiac acceleration occurs at the same time as a high blood-pressure.

It should, however, be pointed out that although this mechanism has been shown to exist it has not yet been shown that the changes in the blood in normal exercise are sufficiently large to be effective in this way, but it is very important in disease.

THE EFFECT OF DRUGS ON THE HEART.

This question belongs properly to the realm of Pharmacology. We shall, therefore, confine ourselves to those substances which are of importance owing to their use in physiological investigation.

We may conveniently divide the drugs which act on the heart into two categories: those which act on the cardio-inhibitory mechanism, and those which act on the cardio-accelerator mechanism.

Adrenaline, from the suprarenal gland, like the sympathetic causes a marked increase in the force and rate of the heart.

Ergotoxine and *ergotamine*, from extract of ergot, by paralysing the sympathetic cause a profound slowing of the heart.

Atropine, from belladonna, causes marked acceleration of the heart-beats, by preventing the action of acetyl-choline normally produced by the vagus. This has already been referred to on p. 85.

Muscarine, from poisonous fungi, *Pilocarpine*, from Jaborandi leaves, *Choline* and the more active *Acetyl-choline* cause marked slowing of the heart. Their action is abolished by atropine.

We have already noted that there is evidence that certain

nerves act by producing adrenaline or acetyl-choline in the region of their nerve-endings.

Nicotine paralyses the synapses of the autonomic nervous system and abolishes, thereby, sympathetic tone and vagus restraint. As the latter predominates, nicotine causes an acceleration of the heart.

Narcotics and Chloroform. Most narcotics, *e.g.* morphine and chloral, if administered in sufficient quantity, depress the sympathetic and lead to increased parasympathetic activity as indicated by cardiac slowing and constriction of the pupils. At a certain stage of their action the cardio-inhibitory reflexes tend to become exaggerated. Complete arrest of the heart may be brought about accidentally in such circumstances. This is well known in chloroform anæsthesia, in which the irritation by the vapour of the lungs may set up inhibitory reflexes. In animals, cutting the vagi immediately sets the heart going again. In man, atropine may be administered to avoid the inhibition. Small amounts of chloroform are, however, quite safe in midwifery cases in which there is an unusual amount of sympathetic activity. Larger amounts of chloroform (over 2 per cent. in the alveolar air), especially if administered for a long time, are liable to act very harmfully on the cardiac muscle.

The Control of the Blood-Vessels—The Vasomotor Nervous System.

The Control of the Blood-Vessels.—The blood-vessels have long been known to change their calibre. This is well seen in the phenomenon of blushing.

The change in diameter is brought about in two ways, nervous and chemical. Normally all blood-vessels are under the control of nerves, but the capillaries are more sensitive to chemical stimuli than larger vessels and they are affected not only by substances circulating in the blood-stream but also, because of their thin walls, by substances which may reach them from the tissue through which they pass.

The control of the blood-vessels has now been shown to be of considerable practical importance, since it has been realised that it may be of great significance in relation to the commonly fatal condition of shock. Operations on nerves to relieve spasm have been commonly performed.

By changing their calibre the vessels distribute the blood to the parts where it is most needed. Thus in physical exercise additional blood is given to the active muscles by dilatation of their blood-vessels, but as the volume of the blood is limited, this can only be done at the expense of other regions, the blood-vessels of which constrict. By means of this control, also the

circulation can adapt itself to the effect of gravity which otherwise would tend to cause the blood to accumulate in dependent parts.

The Vasoconstrictor Centre.—It has now been definitely established that all the blood-vessels in the body are under the control of the vasoconstrictor centre which lies in the floor of the fourth ventricle, a few millimetres above the calamus scriptorius of the medulla. The position of the centre has been discovered by the following means: If sections are made through the brain above this level, there is no immediate effect on the blood-pressure; on the other hand, section of the medulla below this region causes a profound fall of blood-pressure due to the loss of the influence of the centre which normally keeps the vessels in a state of partial contraction or tone (Ludwig and Dittmar).

More detailed localisation has been effected by exploration with electrodes revealing the fact that there is a small area on each side stimulation of which brings about a rise of blood-pressure. It is found that even after the vasoconstrictor centre has been cut off by section of the medulla, recovery of blood-pressure may occur. This suggests that the spinal cord is the seat of subsidiary centres, a view which is supported by the fact that destruction of the cord causes the blood-pressure to fall again.

The vasoconstrictor centre is normally kept stimulated by impulses which reach it by the afferent nerves (especially those from the skin, from the right auricle and probably from the abdomen), and, as first pointed out by Yandell Henderson of Yale, by carbon dioxide in the blood. If, therefore, the afferent end of a sensory nerve is stimulated, a contraction of blood-vessels is brought about and a consequent rise of blood-pressure, although any effect on the heart has been prevented by previous section of its nerves. Reflexes causing rises of blood-pressure are known as Pressor Reflexes. A similar rise of blood-pressure is caused by an accumulation of carbon dioxide in the body, such as occurs in asphyxia (see fig. 118). On the other hand, if an anæsthetised animal is forcibly over-ventilated and the carbon dioxide in the blood reduced there is a fall of blood-pressure which has been shown by Dale and Evans to be due to reduction of the activity of the vasoconstrictor centre. This effect does not, however, necessarily occur in normal man in whom certain compensatory mechanisms are present. The effort of over-ventilation and the effect on the capillaries of washing out the carbon dioxide make up for the reduction of carbon dioxide in the centre. Normally, for example, the skin vessels constrict during over-ventilation (rapid deep breathing) in man. If, however, the individual is immersed in a very hot bath this change in the skin vessels does not occur and over-ventilation may cause a fall of pressure.

The vasoconstrictor centre is, like the heart, also under a considerable restraint from depressor impulses which arise from the cardio-aortic region and the carotid sinus. Cutting off these impulses brings about a vasoconstriction. In this it acts reciprocally with the vasodilator centre, and the vascular constriction when it occurs may be looked upon as partly due to increased vasoconstrictor activity and partly to reduced vasodilator activity.

The most potent stimuli to this centre normally are mental activity, carbon dioxide and a fall of arterial pressure. In exercise such constriction is a protection against a fall of arterial pressure, and in man the skin pallor produced is an important point in the diagnosis of internal hæmorrhage.

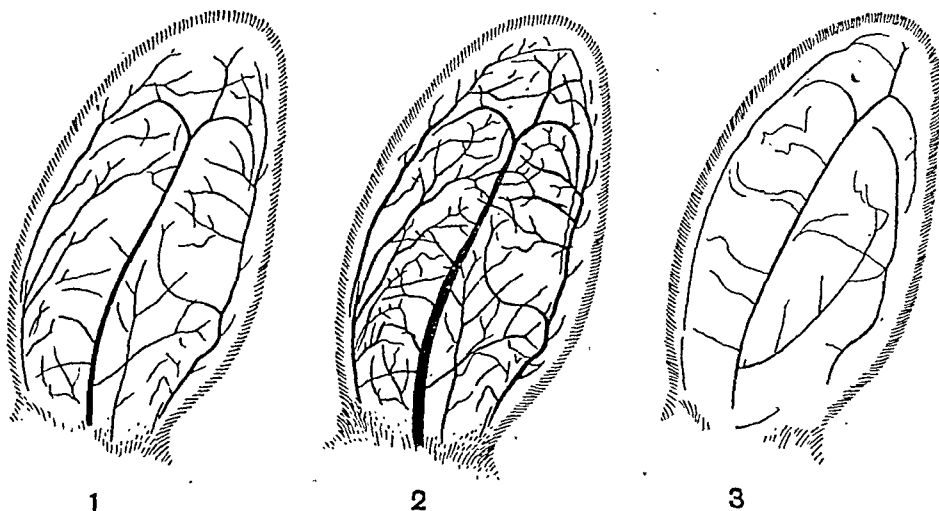


FIG. 82.—The effect of the sympathetic on the blood-vessels of the rabbit's ear. 1, Normal; 2, Sympathetic in the neck cut; 3, Sympathetic stimulated.

How a fall of arterial pressure stimulates the centre is a matter of debate. The centre may be directly sensitive or there may be a reduction of depressor impulses reaching it. (See Hæmorrhage.)

From the vasoconstrictor centre impulses pass down the spinal cord and pass out in the anterior roots to the white rami and thence to the sympathetic chain of ganglia from which they are distributed to the whole body. The reader should refer to the description of the sympathetic nerves given on p. 77. A certain number of fibres pass back by the grey rami and are distributed with the ordinary motor fibres in which they may be demonstrated by the effect of electrical stimulation.

The Vasoconstrictor Fibres.—These fibres, as we have stated, keep the blood-vessels partially constricted, and their function was first demonstrated in 1851 by Wharton Jones of Guy's Hospital, London, in the web of the frog, and Claude Bernard of Paris, in the

ear of a rabbit. He found that division of the cervical sympathetic produced a redness at the side of the head and of the ear in which the central artery and its branches were seen to enlarge and many small branches, not previously visible came into view. The ear felt hotter to the touch. On stimulating the peripheral end of the cut nerve he found that the ear resumed its normal condition and indeed might become paler than usual owing to excessive constriction of blood-vessels.

Wharton Jones showed that sections of the sciatic nerve dilated the vessels of the frog's web and that stimulation caused closure.

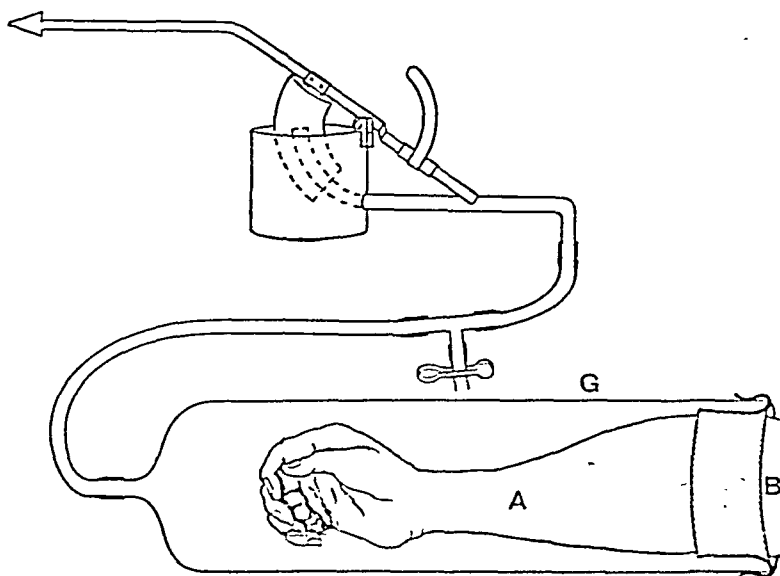


FIG. 83.—Plethysmograph. The arm, A, is enclosed in a glass tube, G, and the system made air-tight with a rubber band, B, fitting around the arm and reflected over the outside of G. The volume changes are transmitted to and recorded by a (McDowall) float-recorder. For short experiments air transmission is used, but for experiments of longer duration the apparatus is filled with water to prevent volume changes due to temperature variations.

Subsequent experiments have shown that the capillaries as well as the arteries are affected by such stimulation (Hooker). It has also been shown that the veins have a vasoconstrictor nerve supply (Donegan).

Evidence of Changes in Blood-Vessels.—Of late years a large amount of research has been made into the control of vessels and various methods have been used to show the delicate changes which may occur in the blood supply of a part, since it is possible only in a very few areas to observe the vessels directly with the naked eye or with the microscope.

The changes which occur and which are recorded when possible are in (1) redness, (2) temperature, (3) flow from the exit vein, (4) venosity of the issuing blood, and (5) the volume of the part.

Recording of the last, known as plethysmography, has been so much used that it is described below in some detail. It must be emphasised, however, that it gives the amount of blood in the part and *not* necessarily the flow through.

Plethysmography. — This method was introduced by Mosso and by its means changes in the volume of a limb or an organ can be recorded graphically. The part is enclosed in an air-tight chamber which communicates with a delicate recorder, as shown in fig. 83. When the part alters in size, air is forced out of the chamber into the recorder or the reverse. Great care has to be taken that in making the air chamber air-tight the vessels entering the limb or organ are not compressed. Plethysmographs are made of glass, metal, *e.g.* Roy's oncometer, or of gutta-percha (Schafer) which is specially useful as it can be readily made to fit any organ. Thus the salivary glands, lobes of the liver or lung, kidney, spleen or coil of intestine can easily be enclosed in an appropriately shaped chamber covered with a glass plate, and made air-tight with vaseline. The use of the plethysmograph is found particularly valuable in relation to the limbs and the intestines, not only for studying the vasomotor nerves but also for investigating the action of drugs on blood-vessels. Changes in the spleen or a coil of the intestine are important as they indicate what is probably occurring in the whole splanchnic area, an area capable of holding a third of the blood of the body. The term *splanchnic area* is applied to the whole abdominal region which is supplied by the splanchnic nerves which pass down from the lower sympathetic ganglia in the thorax. It includes the whole alimentary canal. From what has been said it will be understood that stimulation of either splanchnic nerve causes a constriction of the blood-vessels in this region.

Recent work has shown that changes in the volume of a limb are for the most part due to the skin vessels. If, for example, adrenaline is injected into an animal the normal limb volume is reduced, whereas if the limb is skinned the volume increases because the vessels of muscles are dilated by small doses of this substance.

The rate of the blood-flow through a part is more difficult to measure and it is really much more important than the amount of blood in it. Probably the most accurate way is to find the amount of blood which issues from the vein leaving the part in a given time. For prolonged experiment, however, this involves the use of anticoagulants and the reinjection of the blood. This was originally carried out by Chauveau and Kaufmann in 1886 on the vein of the lower lip of a horse and it was found that mastication increased the flow from four to eight times.

The method of the *thermostromuhr* elaborated by Rein of

Göttingen offers a means of studying the flow in a large vessel without opening it. The piece of vessel is placed between heating plates and the amount of heat taken up by the blood determined by means of thermocouples above and below the heater. This amount depends on the flow. The method of Brodie is also used especially by Lewis, Grant, and others for experiments in man. Here a plethysmograph is placed on the forearm and the arterial flow occluded by means of a sphygmomanometer cuff. Removal of the cuff leads to a swelling of the arm the rate of which is proportional to the rate of blood-flow into it.

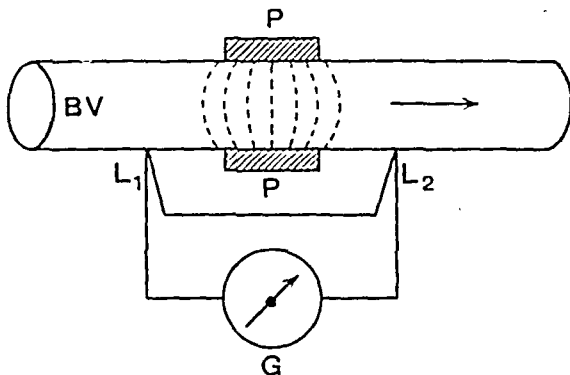


FIG. 84.—Rein's thermostromuhr. Two electrode-plates P held together by a C-bracket are placed on each side of the blood-vessel. The blood is heated by a high frequency current passed between them. The difference in the temperature between the thermo-couples L_1 and L_2 is indicated by the movement of the galvanometer G. (From Rein.)

Thermopiles have also been used, the temperature of the part being proportional to the blood-flow through it. Experiments of this kind have been carried out especially by H. Barcroft.

Perfusion Experiments.—In these experiments there is passed into the artery supplying the part under investigation warm Ringer's solution or blood under constant pressure (about 100 mm. Hg). Changes in the calibre of the vessels are shown by measuring the outflow from the corresponding vein or by recording the resistance to the inflow by means of a side tube. Perfusion experiments have the great advantage that the effect of changes in other parts of the circulation, *e.g.* in the output of the heart, is excluded. The method is specially valuable in the study of the action of drugs.

If a part of the body is perfused while the remainder of the animal is intact, so that the perfused part only communicates with the rest of the animal by means of nerves, it is possible by recording the rate of perfusion to study the activity of the vasomotor-centres.

The Function of the Vasoconstrictor Reflexes and Nerves.—A study of exercise indicates that the function of these reflexes and

nerves is to shut down the blood-vessels of the body generally in order to provide a maximum amount of blood for active tissues. Thus in exercise the splanchnic region is constricted to provide blood for the muscles, while after a meal additional blood is provided for the alimentary canal by constriction of vessels elsewhere.

The Vasodilator Centre.—This centre appears to act reciprocally with the vasoconstrictor centre, *i.e.* when one is stimulated the other is inhibited, and *vice versa*. It lies in the floor of the fourth ventricle close to the vasoconstrictor centre, but it may separately be stimulated electrically and bring about a fall of blood-pressure. Like the vasoconstrictor centre it is constantly sending out impulses.

Normally, it is stimulated by impulses which pass up at each beat of the heart from the cardio-aortic region and the carotid sinus, and which we have seen also bring about slowing of the heart, *via* the vagus (see p. 154). The raising of the pressure in those regions causes a fall of arterial pressure after the heart nerves have been cut while lowering it causes the reverse. The latter effect is probably best seen in the cat by occluding the common carotid artery or by painting the carotid sinus with cocaine especially after the vagi have been cut. A rise of pressure in the abdominal vessels is also effective possibly by stimulating the Pacinian corpuscles.

The vasodilator mechanism may, however, be stimulated in other ways, for example by the application of slow galvanic shocks to many mixed nerves, *e.g.* the sciatic and by many mechanical procedures such as stretching of muscles. These changes are, however, only seen when the sympathetic is depressed by certain anæsthetics. These are important as they may bring about falls of pressure in injury and during surgical operations. All such reflex falls of arterial pressure are known as Depressor Reflexes.

Vasodilator Nerves.—In addition to vasoconstrictor nerves, it seems probable that every organ also receives a supply of vasodilator nerve-fibres. These fibres, when stimulated, cause dilatation of the vessels in the organ supplied. The vasodilator fibres are conveniently divided into several categories—local dilators, posterior root dilators, and sympathetic dilators.

(1) Local vasodilator nerves include such nerves as the chorda tympani to the salivary gland, and the nervus erigens to the erectile tissue of the penis.

(2) Vasodilator fibres were shown by Stricker to pass out from the spinal cord in the *posterior* nerve-roots, stimulation of which caused vasodilatation in the parts supplied, and their existence was amply confirmed by Bayliss. These fibres, like the vagus, are activated in the depressor reflexes from the aorta and carotid sinus. Subsequently they join the mixed nerve-trunks. There is evidence that the

vasodilator nerves to the skin act by liberating vasodilator substances like histamine and acetyl-choline. (See The Autonomic Nervous System.)

(3) Vasodilator fibres also pass out in the sympathetic, but special means have usually to be taken to demonstrate them; for example, the sympathetic may be first paralysed by ergotoxin (Dale) or slow stimuli may be used.

Apparently, however, there is a difference in different animals. Burn obtained dilatation in the hind limb when the abdominal sympathetic was excited by slow stimuli in the dog but not in the cat, while Dastre, Bernard's successor, remarked that had the latter chanced to use a dog instead of a rabbit the vasodilator action of the cervical sympathetic would have been more apparent than its constrictor action.

The sympathetic dilators appear to pass out by the anterior roots and to pass particularly to the vessels of muscles (Gaskell, Cannon).

All dilators reach the organs they supply in mixed nerves in which constrictors commonly predominate. In consequence, stimulation of such a nerve usually causes vasoconstriction.

In order to demonstrate the presence of dilators in mixed nerves special procedures have to be adopted (Bowditch and Warren; Goltz).

1. *The Method of Degeneration*.—If the sciatic nerve is cut, the vessels of the limb dilate. This passes off in a day or two. If the peripheral end of the nerve is then stimulated, the vessels are dilated, as the constrictor fibres degenerate earliest, and so a result is obtained due to the stimulation of the still intact dilator fibres.

2. *The Method of Slowly Interrupted Shocks*.—If a mixed nerve is stimulated with the usual rapidly interrupted faradic current, the effect is constriction; but if the induction shocks are sent in at long intervals (*c.g.* at intervals of a second), vasodilator effects are obtained.

3. *The Influence of Temperature*.—Exposure to a low temperature depresses the constrictors more than the dilators. If the leg is placed in ice-cold water, stimulation of the sciatic, even if it has only recently been divided, produces a flushing of the skin with blood.

4. *Mechanical Stimulation* of a mixed nerve as distinct from electrical stimulation not infrequently causes vasodilatation.

The explanation of these different effects is as yet uncertain, for no difference in the excitability of the vasoconstrictor and vasodilator fibres has been found. It would seem that the effects depend on the number of impulses reaching the vessels.

The Function of the Vasodilator Nerves.

The work of Cannon and his co-workers in Harvard University on the action of adrenaline (see Adrenaline) indicate that the function of the sympathetic vasodilators is probably concerned with the dilatation of the vessels of the muscles in physical exercise.

The function of the dilator reflexes arising from the cardio-aortic

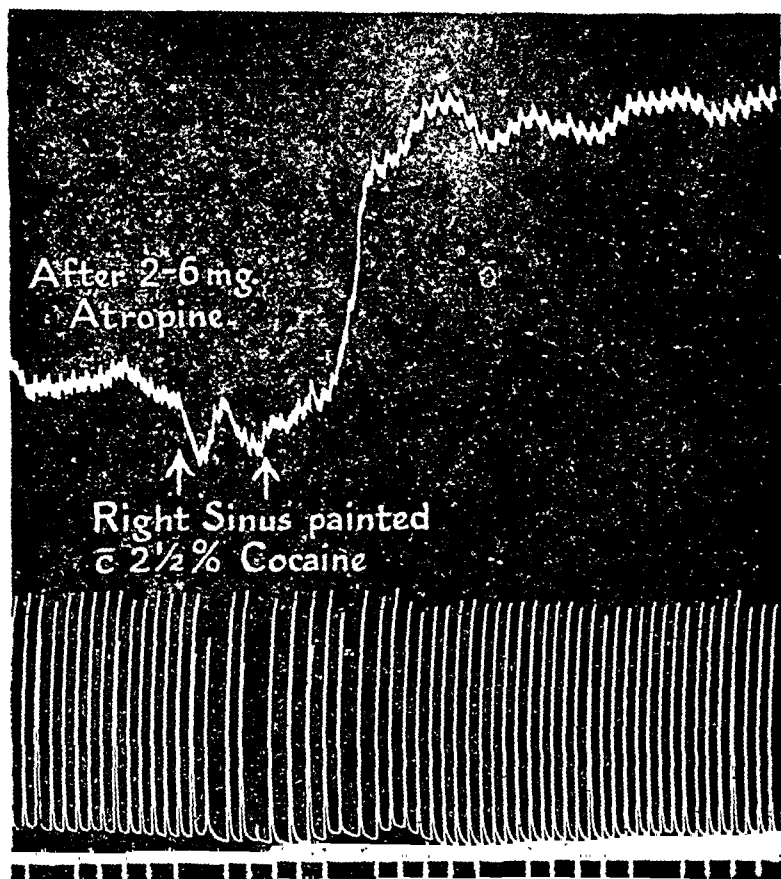


FIG. 85.—The effect on arterial pressure and respiration of paralyzing a carotid sinus by cocaine, the other sinus having been tied off and vagus action avoided by the previous injection of atropine.

region and the carotid sinuses would appear to be twofold. At rest they maintain the arterial pressure at a constant level.

If the carotid sinuses are put out of action by paralyzing them with cocaine, there is a marked rise of the arterial pressure accompanied by a constriction of the peripheral vessels (fig. 85).

In exercise when the blood-pressure rises, however, these reflexes, like the vagal reflexes, appear to be thrown out of action, for it

has been shown (McDowall) that all procedures which accelerate the heart and which are likely to occur in exercise, *e.g.* a rise of venous pressure or adrenaline, cause a reduction or even abolition of the depressor reflexes as they do vagus activity.

Since it has been shown that stimulation of the carotid sinus (see fig. 86) or of the central end of the depressor nerve causes a

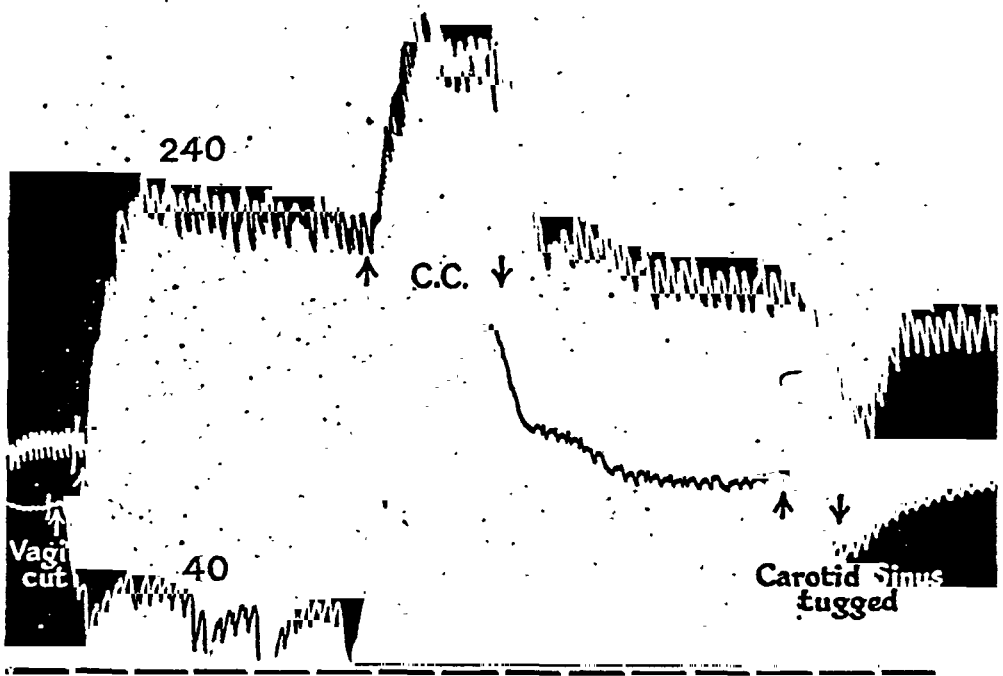


FIG. 86.—Records of arterial and venous pressures. At the first arrow is seen a rise of arterial pressure and a fall of venous pressure as a result of section of the vagi including the aortic depressor nerves. The rise of arterial pressure is due partly to an increased rate and output of the heart and to vasoconstriction. The fall of venous pressure is due to the increased cardiac output depleting the venous reservoir. At C.C. the carotid sinuses were clipped off; there is a further rise of arterial pressure partly from the same causes as before, but in addition there is diminution of the capacity of the circulation and a rise of venous pressure which increases the output of the heart. Later stimulation of the sinus by tugging caused an increased capacity of the circulation.

greatly increased capacity of the circulation (Bayliss) and since experimental interruption of the reflexes increases the venous flow and the output of the heart, it is probable, therefore, that an important function of these vasodilator reflexes is to maintain a large volume of blood immediately available for the active muscles during exercise. Thus the vagal reflexes and the capacity reflexes which have a similar origin are both concerned with increasing the degree of change in the rate of the circulation which is possible in exercise.

Differences between Stimulating the Central and Peripheral Ends of the Vagus.

Stimulation of the centres is responsible for the difference between the effect of stimulating the central and peripheral ends of the vagus.

If the peripheral end is stimulated the heart is slowed and the blood-pressure falls abruptly, but recovers very sharply to above its previous level as soon as the stimulation ceases, because blood has banked up in the veins.

If the vagi are both cut the fall of pressure produced by stimulation of a central end is due to stimulation of the vasodilator and inhibition of the vasoconstrictor centres. Since it is vascular, therefore, the fall and recovery are slow and capacity effects have prevented any banking up of blood in the veins.

If one vagus is left intact the effects of stimulating the central end of the other are intermediate.

The Chemical Control of the Blood-Vessels.

This control is both central and local. We have seen that carbon dioxide stimulates the vasomotor centre and that, in relation to the capillaries, this substance and lactic acid cause dilatation of these vessels. These chemical substances, produced locally, take precedence over nervous influences, for when the cervical sympathetic is stimulated the constrictor effect is seen to wear off as soon as the ear becomes asphyxiated. The importance of these facts is dealt with below. According to Fleisch the arterioles may also participate in this local chemical control.

THE EFFECT OF EXERCISE ON THE CIRCULATION.

The various changes are described as being actually brought about by exercise, but, as we shall see later, some of them may anticipate the exercise. This is especially true also of the secretion of adrenaline, which assists the nervous control to redistribute the blood according to bodily needs. (See Adrenaline.)

Local Vascular Changes.—We now know from the work of Krogh (Professor of Zoophysiology in Copenhagen) that the capillaries can alter their calibre independently of the arterioles, and that, like the latter, they are supplied with nerves (Hooker, see Capillary Circulation, p. 142).

When exercise takes place, there is marked dilatation of capillaries in the active region. This has been most convincingly demonstrated by Krogh. By injecting indian ink into the blood-vessels of two sets of frogs, in one of which the tongues had been stimulated to contract for some time previously, he found on examination of

sections that many more capillaries could be seen in the active muscle than in the resting tissue.

What causes this dilatation has been a matter of some debate. The venous blood leaving a tetanised limb contains a variety of vasodilator substances of which the most important are carbon dioxide, lactic acid, histamine, and adenosine triphosphate (Fleish and Weber, 1937). The same substances accumulate locally and are released into the venous blood if a part is asphyxiated by obstructing its arterial supply, and as might be expected, extensive tetanisation of muscles leads to a state like histamine shock.

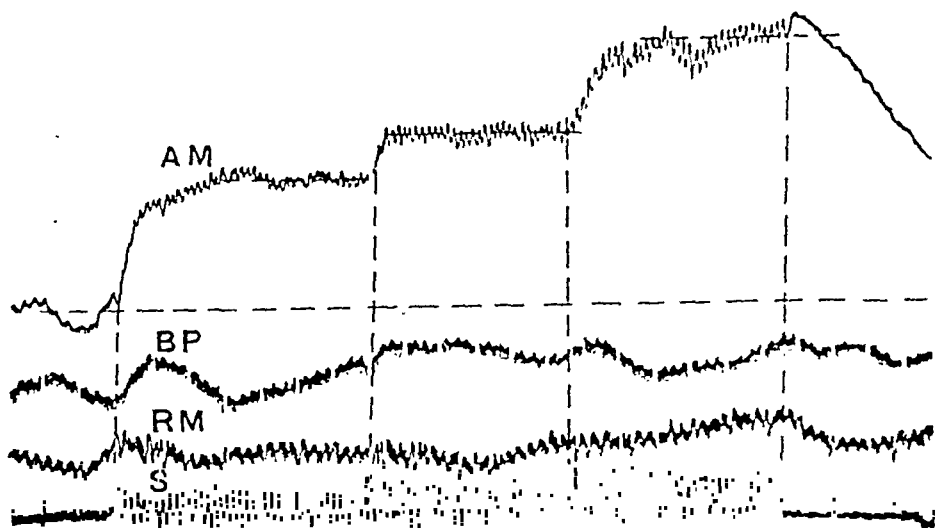


FIG. 87.—Records taken by the thermostrohr. S, the amount of stimulation applied to the limb. AM, the increased blood-flow produced in it. RM, the blood-flow in the resting muscles of the opposite side. BP, blood-pressure. (Redrawn from Rein.)

The suggestion that histamine was concerned was first made by Lewis and by Anrep, but more recently Feldberg has found that tetanisation results in a secretion of gastric juice, a fact which supports the suggestion and which may be of considerable practical importance as physical rest is known to be an important therapeutic measure in cases of gastric ulcer.

The actual changes which take place in the blood-flow in a muscle during and after exercise have been studied by Anrep and by Rein. During a severe tetanus the blood-flow through a muscle may cease, but immediately afterwards there is a greatly increased flow because of the diminished peripheral resistance. During rhythmic stimulation the flow is greatly increased, as shown in fig. 87.

At the same time, impulses appear to pass up the sensory nerves from the active tissues and bring about dilatation of the vessels supplying the part. This is suggested by the work of Lovén, who

found that if the afferent nerve from an organ was stimulated, dilatation of the vessels in that organ was brought about reflexly, although there was at the same time a rise of arterial blood-pressure.

General Vascular Changes.—While there is a local dilatation of vessels it is found that there is, provided the exercise is sufficiently severe, a rise of systolic blood-pressure. The diastolic pressure rises less. This rise is almost entirely brought about by the mental effort concerned since exercise without such effort may result in a fall and the rise in exercise is little greater than that produced by mental effort alone. The rise may be enhanced by stimulation of the vasomotor centre by afferent nerves and by carbon dioxide produced by the active muscles.

At the commencement of the exercise the rise is due to an increased peripheral resistance and an increased cardiac output. As the exercise proceeds the diastolic pressure may actually fall because of the dilated vessels. The increased cardiac output is, however, maintained by a rise of venous pressure and an increased return of blood to the heart.

The increased flow through the active muscles, together with the reduction of the capacity of the blood depôts, raises the venous pressure and this is enhanced by the compression of the valved veins. The occurrence of a rise of venous pressure in exercise was first found by Hooker and has been amply confirmed. At the same time the carbon dioxide, as we shall see later, stimulates respiration, which is such an important factor in causing a return of blood to the heart that it is referred to as the respiratory pump. At each inspiration the descent of the diaphragm raises the pressure in the abdomen, similarly the intrathoracic pressure is reduced and blood is, therefore, drawn into the thorax.

The moment the exercise ceases the blood-pressure falls immediately as seen in fig. 88, p. 170. After bouts of severe and prolonged physical training, such as that of commando units, the systolic blood-pressure may remain low, *e.g.* 80 mm., for some time.

Cardiac Changes.—The increased return of the blood to the right side of the heart brings about a large increase in the cardiac output per minute which may be more than six-fold. This occurs: (1) in virtue of the increased filling, which increases the output per beat (see Output of Heart); and (2) because of the increased heart-rate, which is brought about partly as a result of direct action of increased venous pressure and warmer blood on the pace-maker, but chiefly through the nervous mechanism of the heart.

There is a diminution of the normal vagus restraint of the heart and increased sympathetic activity. This is probably due to a variety of causes partly and initially *psychic*, but continued by

reflex action once the exercise is begun. The latter effects are produced partly by the stimulation of afferent nerves in the active tissues; but an important mechanism concerned is the *Bainbridge or right auricular reflex*.

The Bainbridge or Right Auricular Reflex.—When the pressure in the right auricle rises, impulses pass up the vagi to the medulla to inhibit the cardio-inhibitory and to stimulate the

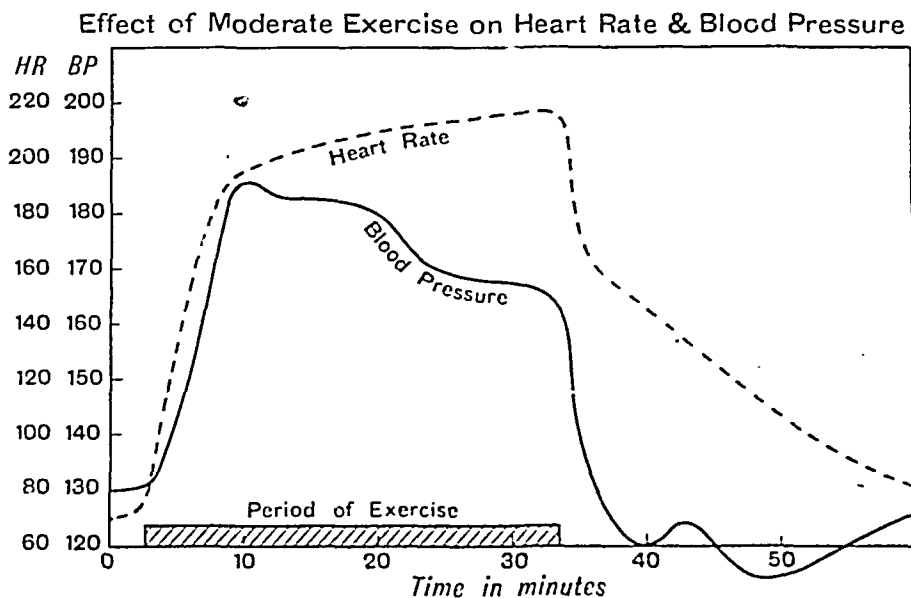


FIG. 88.—Note the rapid rise of the B.P. and H.R. at the commencement of the exercise and the rapid fall even to below normal of the B.P. at the cessation. The fluctuations are probably reflex in origin. (After Bowen.)

cardio-accelerator mechanism, with the result that the heart-rate increases. This was first demonstrated by Bainbridge,* who injected saline into the veins, and it has since been shown that distension of a small balloon in the auricle has the same effect. If the vagi are cut, the same degree of cardiac acceleration does not occur, but since some acceleration occurs after atropine, which paralyses the vagus-endings, it is evident that it is not wholly the reduction of efferent impulses of the vagus which is concerned. It is assumed then that the afferent pathway of the reflex arc is the vagus nerve, and, since cutting the sympathetic nerves still further reduces the acceleration, it is assumed that normally there is not only a reduction of vagus restraint, but also an increased sympathetic activity.

After a short spell of gentle exercise in a healthy adult the

* Bainbridge (1918) was Professor of Physiology at Newcastle and at St Bartholomew's Hospital.

heart-rate returns to a rate lower than its previous resting value presumably because of increased activity of the cardio-inhibitory reflexes—this after slowing becomes cumulative.

Central Effects.—There is also evidence that the oxygen-want may cause a direct central stimulation of the sympathetic and a reduction of the normal vagus restraint, thus making it possible for the heart to accelerate in spite of the high blood-pressure and the depressor reflexes.

In very severe exercise the rate and force of the heart may be still further increased by the secretion of **adrenaline** from the suprarenal glands, but that this does not account for all the above results is shown by the fact that they occur after the glands have been tied off.

The Effects of Temperature.—Subsequently, if the exercise is prolonged, the body temperature tends to rise and the hot blood stimulates the heat-regulating centre and causes dilatation of the skin vessels. At the same time there is an increased activity of the sweat glands, the metabolites of which also affect the vessels in their vicinity.

The Effects of the Higher Centres.—Even before exercise begins there is an acceleration of the heart and a general constriction of vessels, but how this effect of the higher centres is brought about is far from clear. Mental activity alone will bring about similar effects, causing in some individuals a rise of pressure of 50 mm. Hg above normal. Even minute amounts of mental effort were shown by Mosso to cause a diminution in limb volume. This has been amply confirmed and it is considered that the diminution of the electrical resistance of the skin, the so-called *psychogalvanic reflex*, which accompanies such effort, is due to this vasoconstriction, for it has been shown that all circumstances which cause vasoconstriction of the skin (*e.g.* the injection of adrenaline or pituitrin or cold applied to another part of the body) cause a similar fall in the electrical resistance.

It has been suggested that the sweat glands are concerned in the reaction, but Waller has shown that atropine does not abolish the reaction, and profuse sweating does not cause such a fall unless the skin has been dry. It is probable, however, that if the sweat glands and the vessels thereto are absent, as sometimes occurs, the reaction also is absent. The suggestion that the reaction is not really due to a change in resistance is negated by the observation that it occurs if an alternating current is used in the determination of the resistance. Changes in electrical potential also take place, but unlike the changes of resistance are not abolished if the limb is emptied of blood by bandaging.

The electrical resistance depends on the superficial layers of the epidermis (Lewis and Zottermann), which according to Densham are deformed by the vasoconstriction of the underlying vessels of the dermis. Since similar changes occur on sensory stimulation in

animals and in man, if such stimulation is merely threatened the so-called effects of the higher centres may be looked upon as being in some way due to a "conditioned sensory stimulation."

The vascular effects of emotion are by no means confined to the skin. It has been found possible to keep the spleen or the colon of a dog outside the abdominal wall. The epithelium rapidly grows over it and the animal suffers no discomfort (Hargis and Mann, Barcroft and Stevens, Drury and Florey). In states of emotion the spleen and the vessels of the colon are seen to constrict.

The Effects of Training.—As might be expected, training makes the circulation more efficient, a fact which is particularly well seen in relation to the output of the heart, which in the very highly trained athlete is stated to reach the astounding figure of 30 litres per minute during severe exercise. The size of the heart as seen by X-rays is increased.

The increase is brought about more by an increased output per beat than by an increased heart-rate; indeed, exercise increases the heart-rate less in the trained than in the untrained man. We have already noted that the heart-rate is markedly slower in the former, presumably the result of an increased activity of the general depressor reflexes from the carotid sinuses and cardio-aortic regions. It is probable, too, that the vascular component of the depressor reflexes is also increased; that is, the total capacity of the circulation and total blood volume is increased. The effect of training on the circulation is seen in relation to the output of the heart.

	Minute-output of heart.	Output per beat.	Pulse-rate per min.	Coefficient of utilisation.
Untrained . .	4.8 litres	62 c.c.	77	0.30
Trained . .	5.65 "	103 "	55	0.26

The above figures were recorded by Lindhard from the same individual at rest before and after training. (Bainbridge, Schneider.)

EFFECT OF GRAVITY ON THE CIRCULATION.

The main effect of gravity is that the blood tends to accumulate in the veins of dependent parts. Thus, if an animal is placed suddenly with its legs hanging down, less blood returns to the heart, and the blood-pressure in the arteries falls temporarily in consequence. If the vasomotor system is acting properly, however, the blood-pressure rapidly returns to normal as the fall of blood-pressure together with the partial cerebral anaemia causes stimulation of the heart and of the vasomotor centre and vaso-

constriction of the splanchnic area. If the vasomotor centre is inefficient, the cardiac acceleration is all the more marked. Leonard Hill* suggests that this might be used as a test of vasomotor efficiency. At the same time increased respiration causes an increased return of blood to the heart (see Effect of Respiratory Movements on Circulation).

	UNTRAINED.			TRAINED.		
	Lying.	Sitting.	Standing.	Lying.	Sitting.	Standing.
HR	72	76	80	60	65	72
BP	115	118	120	120	130	134

The effect of change of posture on the heart-rate (HR) and blood-pressure (BP) of healthy young adults. Great individual variability occurs.

A very striking illustration of the effect of gravity on the circulation can be demonstrated on the eel. The animal is anæsthetised, and a small window is made in the body wall to expose the heart. If the animal is then suspended tail downwards, the beating heart is seen to be empty of blood; all the blood accumulates in the tail and lower part of the body; the animal has no "respiratory pump," such as a mammal possesses, to overcome the effects of gravity. If, however, the animal, still with its tail downwards, is suspended in a tall vessel of water, the pressure of the water outside its body enables it to overcome the hydrostatic effect of gravitation, and the heart-cavities once more fill with blood during every diastole. Another experiment was originally performed by Salathé on a "hutch" rabbit. If the animal is held by the ears with its legs hanging down, it soon becomes unconscious, and if left in that position for about half an hour it will die. This is due to anæmia of the brain; the blood accumulates in the very pendulous abdomen which such domesticated animals acquire, the vasomotor mechanism of the splanchnic area is deficient in tone, and cannot be set into such vigorous action as is necessary to overcome the effects of gravity. Consciousness is, however, soon restored if the animal is placed in a horizontal position, or if while it is still hanging vertically the abdomen is squeezed or bandaged. A wild rabbit, on the other hand, suffers no inconvenience from a vertical position; it is a more healthy animal in every respect; its abdomen is not pendulous, and its vasomotor power is intact.

It may be shown that carbon dioxide is necessary for the adequate response of the vasomotor centre to posture (McDowall). An animal may respond perfectly if the carbon dioxide is normal, but if it is over-ventilated it no longer responds. Some persons show the same reaction.

* L. Hill was Professor of Physiology at the London Hospital.

The transient giddiness experienced after an illness on assuming the erect posture is due to similar cerebral anæmia. The debility following influenza is in part due to this cause; in some instances the arterial pressure, although normal in the horizontal position, falls to under 80 in the erect posture.

THE EFFECT OF CENTRIFUGAL FORCE.

Centrifugal force equivalent to several times that of gravity may affect pilots of aircraft when making rapid turns. The sudden fall of blood-pressure produced causes a visual black-out which may be counteracted by abdominal compression.

THE EFFECT OF HÆMORRHAGE.

The effects of hæmorrhage depend on its severity and its duration, and are important as by them the clinician diagnoses internal hæmorrhage.

If a small amount of blood is removed from the body there is a temporary fall of arterial blood-pressure during the removal from which there is rapid recovery. This recovery is due largely to increased activity of the vasomotor centre. How the centre is stimulated is not quite certain. It has been common to explain the increased activity as the result of a reduction of depressor impulses from the carotid sinus and cardio-aortic region. This does not, however, occur unless the hæmorrhage is very severe; indeed small degrees of hæmorrhage increase the activity of the depressor reflexes. It has also been shown that after hæmorrhage pressor impulses pass up the vagus (McDowall). The presence of such pressor fibres in the vagi is shown by the fact that after severe hæmorrhage section of the nerves causes a fall of arterial pressure (Pavlov). The activity of the vasomotor centre causes the spleen to constrict and to throw into the circulation its reserve of blood. It causes also constriction of the vessels of the intestine and of the skin, which leads to obvious pallor. This constriction of vessels increases the peripheral resistance and hence the large fall of venous pressure which persists much longer than the arterial fall.

This fact is probably of considerable practical value as bleeding may be used as a therapeutic measure to reduce the work to be done by a weak heart.

If the hæmorrhage is severe the recovery process is slower, but the blood volume is rapidly made up from the tissue fluids which enter the blood as a result of the fall in capillary pressure. If the hæmorrhage is repeated over a period of weeks the yellow marrow of the bones becomes red through increased activity and commences to form blood-corpuscles.

The heart-rate is usually increased by hæmorrhage as a result of a reduction in the impulses which normally depress the heart *via* the vagus centre. In severe hæmorrhage the oxygen-lack produced also stimulates the sympathetic, but there are several points in relation to the cause of the increased heart-rate which still need investigation.

It has been found, however, that in many donors at blood-depôts the heart becomes slow when half a pint of blood is removed, but this may be psychological.

The respiration, we have seen, at first becomes deeper and more rapid; it then changes its character, inspiration being more prolonged (air hunger). Finally, there is gasping and the centre fails. The initial increased activity (air hunger) greatly aids the return of blood to the heart (see Effect of Respiration on Circulation).

Unless a large vessel is opened hæmorrhage is for various reasons seldom fatal. The damaged blood-vessel retracts and contracts, and this, together with the clotting of the blood, tends to close the opening, while the formation of the clot is facilitated by the fall of arterial pressure. For these reasons a section even of such a large vessel as the radial artery may not cause death.

The extensive practice of bleeding, usually about $\frac{3}{4}$ pint, for the collection of blood for transfusion purposes in war-time has led to an extensive study of the changes which take place in man. These are almost the same as occur in animals, but often there is no active sympathetic reaction but the reverse, with a slowing of the heart, fall of blood-pressure, and fainting. How far this is psychological and how far it is due to loss of activity of the vasomotor centre consequent on overbreathing, or the actual loss of blood, has not been decided. There is great individual variability.

Local Peculiarities of the Circulation.

The Coronary Circulation.—A separate blood supply to the heart is peculiar to animals above the reptiles. In mammals the amount of the coronary flow is remarkable, and it is estimated that it takes about a quarter of the total cardiac output.* This has been ascertained in a heart-lung preparation (*q.v.*) in which it is easy to measure the output by collecting the blood as it flows from the coronary sinus by means of a special cannula. The rate of inflow may also be studied by supplying the coronary vessels of a beating heart with blood from a reservoir and recording by means of a rapidly acting optical recorder the interruption to the flow caused by the beat of the heart (Wiggers). The flow in the coronary arteries practically ceases during the systole of the heart which

* It is doubtful if this figure holds for the intact animal although it is true of the heart-lung preparation (Anrep).

can be looked upon as massaging the coronary circulation, the flow from the venous sinus being greatest at the beginning of systole (Anrep).

As in muscles generally the flow is increased by exercise, by oxygen-want, and to a lesser extent by excess of carbon dioxide. In exercise it is calculated that the flow may amount to as much as 14 litres per minute.

The flow varies according to the mean aortic blood-pressure. Anrep and Segall found that a rise of pressure from 50 to 130 mm. Hg would cause a rise from 20 to 250 c.c. per minute in the denervated heart-lung preparation. As the cardiac output increases, so also does the flow when the cardiac nerves are intact.

The vessels are constricted by stimulation of the vagi and dilated by sympathetic stimulation or by adrenaline. The muscle of the heart then appears in this respect to be little different from the voluntary muscles which it serves.

The Pulmonary Circulation.—A consideration of this circulation is deferred until respiration has been studied, as it is profoundly affected by the respiratory movements.

The Cerebral Circulation.—The brain must always be supplied with blood, for otherwise immediate loss of consciousness would follow. Four arteries—two carotids and two vertebrals—are supplied to the brain, and these anastomose together in the circle of Willis. Two of the brain arteries can be tied in monkeys, and three or even all four in dogs, without the production of serious symptoms. In the last case enough blood reaches the brain by branches from the superior intercostal arteries to the anterior spinal artery. In man the sudden occlusion of both carotids causes loss of consciousness.

The large venous trunks or sinuses are formed so as to be scarcely capable of change of size, surrounded, as they are, by the tough tissue of the dura mater, and, in some instances, bounded on one side by the bony cranium. There are no valves between the vertebral veins and the vena cava, and hence any raising of the general venous pressure in the thorax or abdomen is communicated to the brain, a fact which no doubt contributes to the occurrence of cerebral hæmorrhage when straining at stool.

Since the brain is enclosed in the rigid cranium, it used to be thought that the quantity of blood must be the same at all times and that changes in the blood-flow must be dependent on the condition of vessels in other parts of the body. The arteries, however, have muscular walls and are supplied by nerves.

In 1928 Forbes and Wolff, by introducing a window into the skull in order to maintain the normal environment of the vessels, were able to observe that the vessels contract when the cervical

sympathetic is stimulated and dilate on stimulation of the central end of the vagus. Indeed, the cerebral vessels have been shown to react to various procedures exactly as do the vessels elsewhere. The exact significance of these facts is not quite clear. It may be that when a local change in the vessels takes place there is compensatory change in other parts, or it may be that the cerebral fluid within the cranium may change appreciably in quantity. It seems possible that when one part of the brain is active, other parts of the organ become less active; indeed, it is common experience that we cannot use the whole of the brain at once. The physiology of attention may depend on these facts. Of interest in this respect is the observation that the intravenous injection of hypertonic saline causes a distinct reduction of the volume of the brain.

These experiments confirm the observation of Claude Bernard, who found an increase of brain temperature on section of the cervical sympathetic. Several workers, *e.g.* Cyon and later Wiggers, have demonstrated that the vessels are constricted by adrenaline.

At the same time the cerebral circulation is profoundly influenced by the general blood-pressure. If this falls, the blood-flow through the brain may be so reduced that unconsciousness occurs, as in fainting, when the vessels of the body generally become dilated.

It is not the volume of the blood in the brain so much as the velocity of its flow which is altered by changes in the general circulation. If the aortic pressure rises and the vena cava pressure remains constant, there is increased velocity of flow. While if the aortic pressure remains constant and the vena cava pressure rises, there is diminished velocity of flow.

The brain presses against the cranial wall with a pressure equal to that in the cerebral capillaries. A foreign body introduced within the cranium, such as a blood-clot or depressed bone, produces local anæmia of the brain, by occupying the room of the blood. So soon as the capillaries are thus obliterated the pressure is raised to arterial pressure. The serious results that follow cerebral compression are primarily due to obliteration of the capillaries, and consequent anæmia of the brain. A very small foreign body will, if situated in the region of the bulb, produce the gravest symptoms, for apart from trauma it may cause anæmia of the centres which control the vascular and respiratory systems. The cerebral hemispheres may, on the other hand, be compressed to a large extent without causing a fatal result.

Hæmorrhage from a fractured skull may cause the brain to be forced downwards and compress the medulla against the foramen magnum. When compression occurs from any causes a sequence of events may occur. First the centres are stimulated, vasomotor, cardio-

accelerator and cardio-inhibitory—in that order—and later they all are paralysed, together with the respiratory centre, and death results if the compression is not relieved.

The Cutaneous Circulation.—The circulation through the skin is of special importance as many of the changes which occur in it are visible to the naked eye and are important in the diagnosis of disease. The changes which occur affect its colour and temperature.

The blood-vessels of the skin consist of two plexuses, a sub-papillary plexus which sends capillary loops into the skin papillæ (see skin), and a sub-dermal plexus. No vessels pass to the epidermis, but if this is rendered transparent by oil the capillary loops may be seen through it. Apart from pigmentation, it is the amount and quality of the blood in the sub-papillary venous plexus which determines the colour of the skin. The following conditions may occur.

1. The arterioles, capillaries, and venules may be constricted. This causes the skin to be pale and cold and occurs typically in hæmorrhage and in shock. This occurs because the skin, especially the sub-papillary plexus, is one of the important blood-depôts of the body and in man may contain 1 litre of blood. Exposure to cold, which constricts the skin vessels and probably others, may increase by direct action and reflexes the output of the heart by as much as 50 per cent. The vessels of the skin appear to be kept open largely by the pressure of the blood within them, for they constrict when the activity of the vasomotor centre is reduced and the vessels of the body generally dilate as in the ordinary faint. A less marked pallor occurs when there is a deficiency in hæmoglobin in the blood.

2. The arterioles, capillaries, and venules may be dilated. This causes the skin to be red and warm. It occurs typically in inflammation and after irritation of the skin.

3. The arterioles and venules may be dilated but the capillaries constricted. This causes a hot pale skin, which occurs sometimes in fevers and after loss of the nerve supply, since the capillaries but not the arteries may regain their tone.

4. The arterioles and venules may be constricted but the capillaries dilated. This causes a cold blue skin, since blood trapped in the skin capillaries loses its oxygen. It occurs in the extremities when exposed to severe cold and represents an attempt of the body to conserve heat.

Whether the skin is blue or pink when the circulation is normal depends on the colour of the blood itself, and particularly on the amount of reduced hæmoglobin in the arterial blood. When the total hæmoglobin of the blood is low as in anæmia the patient is pale and even in mild asphyxial states does not become blue, since the amount of reduced hæmoglobin is not sufficient to produce this colour.

Mottling of the skin is seen in many fevers and is considered to be due to the patchy nature of the circulation. A mottling of the skin over the shins can be produced by sitting too close to an open fire. This is popularly known as "Granny's tartan."

The Response of the Skin to Mechanical Injury.

If the skin in a normally unexposed part is stroked with a blunt object a white line is produced, but if the stimulus is just slightly more severe it is followed rapidly by a red line. The first is due to mechanical stimulation and contraction of the capillaries and the second to the local production of a chemical substance (like histamine, Lewis). This is shown by the fact that the duration of the reddening is affected by the rate of circulation through the part. In some persons with sensitive skins the reaction may be much more severe and actual wheals may be produced.

Outside the area stroked appears a red flare or flush. This, since it is abolished by nerve section or anæsthetisation, has been shown to depend on nervous reflexes. The complete phenomenon terminating in whealing is called the **triple response**.

In normal persons a number of procedures may bring about whealing and blistering of the skin, *e.g.* excessive heat or cold or mechanical injury. The evidence is very complete that the blister is produced as a result of the similar release of a histamine-like substance which dilates the capillaries and causes their walls to be abnormally permeable so that the fluid of the blood seeps through too rapidly.

Erectile Structures.—The instances of greatest variation in the quantity of blood contained, at different times, in the same organs, are found in certain structures which, under ordinary conditions, are soft and flaccid, but, at certain times, receive an unusually large quantity of blood, become distended and swollen by it, and pass into the state which has been termed *erection*. Such structures are the *corpora cavernosa penis* and *corpus cavernosum urethræ* in the male, and the *clitoris* in the female. The *corpus cavernosum penis*, which is the best example of an erectile structure, has an external fibrous membrane or sheath; and from the inner surface of the latter are prolonged numerous fine lamellæ which divide its cavity into small compartments. Within these is situated the plexus of veins on which the peculiar erectile property of the organ mainly depends. It consists of short veins which very closely interlace and anastomose with each other in all directions, and admit of great variations of size, collapsing in the passive state of the organ, but capable of an amount of dilatation which exceeds beyond comparison that of the arteries and veins which convey the blood to and from them. The strong fibrous tissue lying in the intervals of the venous plexuses, and the external fibrous membrane or sheath with which it is connected, limit the distension of the vessels, and during the state of erection, give to the penis its condition of tension and firmness. The same general condition of vessels exists in the *corpus cavernosum urethræ*, but around the urethra the fibrous tissue is much weaker than around the body of the penis, and around the glans there is none. The venous blood is returned from the plexuses by comparatively small veins. For all these veins one condition is the same; namely, that they are liable to the pressure of muscles when

they leave the penis. The muscles chiefly concerned in this action are the erector penis and accelerator urinæ. Erection results from the distension of the venous plexuses with blood. The principal exciting cause in the erection of the penis is psychological but it may also be produced by irritation, originating in the part itself, and derived reflexly from the brain and spinal cord. The nervous influence is communicated to the penis by the pudendal nerves, which ramify in its vascular tissue; and after their division the penis is no longer capable of erection.

Erection is not complete, nor maintained for any time except when, together with the influx of blood, the muscles mentioned contract, and by compressing the veins, stop the efflux of blood, or prevent it from being as great as the influx.

The Magnitude and Variability of the Arterial Pressure.

In view of the ease with which blood-pressure may be determined and the practical importance of the subject, we may now summarise the factors which determine and vary its magnitude.

1. *The Peripheral Resistance.*—This may be reduced by removal of the nervous control of the blood-vessels, or by the action of chemical substances. It is increased similarly by any means which constrict the peripheral vessels.

2. *The Elasticity of the Vessels.*—No change occurs physiologically but in disease and in old age the vessels may degenerate and become less extensible. An associated reduction of calibre leads to a high blood-pressure.

3. *The Output of the Heart.*—This in turn depends on: (a) the efficiency of the heart; (b) the venous return. A marked reduction in either causes a fall of arterial pressure if severe, but lesser degrees are compensated for by an increase in the peripheral resistance and a diminution in the capacity of the circulation. From the point of view of clinical medicine it is important to note that in slow heart failure the blood-pressure falls only towards the end. The factors which vary the venous return have already been discussed and may now be summarised. They are: the amount of blood in the body, the capacity of the circulation especially of the veins and capillaries, the amount of blood reaching the veins from the arteries, the respiratory movements, and capillary compression in exercise.

The Efficiency of the Circulation.

Many attempts have been made to arrive at some standard by which the efficiency of the circulation may be measured, since failure of the circulation, especially of the heart, is a common concomitant of disease and limits capability for work. The difficulty is that muscular capability varies very much, and what may be strenuous exercise to one subject may be negligible to another. All such tests attempt to ascertain the tolerance of the heart to effort.

The **Effort Tolerance Test** was introduced by Cotton and Lewis, 1918, and as used by Schneider consists of stepping on and off

a stool $18\frac{1}{2}$ inches high 5 times in 15 seconds and recording the time taken for the pulse to return to normal. This mild exercise causes a moderate rise in the heart-rate but there is a rapid return to normal. If the heart does not return to normal in 1 minute (*i.e.* does not get rid of the increased venous pressure) it is probably inefficient. In all such tests it is essential that the subject should be at physical and mental rest before commencing the test.

The 40 Millimetre Test.—In the Royal Air Force the 40 mm. test is used. In this test the subject after a deep breath blows (with his nose clipped) into a mercury manometer and maintains its level at 40. A fit subject should maintain this pressure for 52 seconds and show no change in blood-pressure or heart-rate until he reaches "breaking point." The test is purely arbitrary and is somewhat difficult to analyse, as it involves respiratory acid-base and mental as well as circulatory considerations.

The response to posture may also be taken as an indication of circulatory efficiency (Leonard Hill, 1894). The more efficient the circulation the less is the increase of the heart-rate when a recumbent subject assumes the erect posture. In efficient persons the heart-rate does not increase on standing nor should there be any fall of arterial pressure, indeed there is commonly a rise of 5-10 mm. of mercury. The test has been elaborated by Crampton in America who devised a scale by which an efficiency index was arrived at.

Turner has elaborated the test still further and in arriving at an index takes into consideration the reclining pulse-rate, the pulse pressure, the diastolic pressure, and the effect of prolonged *quiet* standing (15 minutes).

The Oxygen Consumption Test.—This test has not been much used, but from the work of Hemingway and his colleagues it would seem that it is probably the best test in fit persons—in whom the oxygen-uptake should reach 2000 c.c. per minute, but may actually reach 5000 c.c. It is a combined test for the hæmo-respiratory system.

All such tests may be supplemented by noting the effect of a moderate exercise on respiration and the sensations of the subject generally.

CHAPTER XV

THE BLOOD DEPÔTS

It has now become clear that all the blood in the body is not in active circulation. Some is circulating slowly or may even be stagnant in certain parts. It is, however, readily available should necessity such as imposed by exercise or hæmorrhage demand.

One of the most important depôts is the **skin**. The pallor of the skin in illness and particularly in hæmorrhage, especially if the hæmorrhage is internal, has an important diagnostic value. It is probable that practically all the organs of the body participate with the possible exception of the brain, heart and muscles. Another important depôt is the splanchnic region, including the liver, and according to some workers the lung can act in this way.

As we have seen in relation to the control of the circulation, it seems probable that a chief function of the general vasodilator reflexes is the maintenance of the blood depôts at adequate capacity. It would seem that the spleen has a special function as a depôt and it is therefore considered separately.

The **Spléén**, which lies to the left of the stomach, is a sponge-like organ covered with a fibro-elastic smooth muscular coat from which trabeculæ of muscular and fibrous tissue run to the interior. Its histological appearance gives but little clue to its function, because at death it is in a state of extreme contraction. Although many red blood corpuscles are seen in the usual histological sections, white blood corpuscles predominate, and the organ has the general appearance of a lymph gland in which are placed the characteristic Malpighian corpuscles, which are aggregations of white cells around growing centres, but the differences in its appearance from time to time led Gray the anatomist in 1854 to describe it as a storehouse for blood. This was amply confirmed by Barcroft and others who were led to the study of the organ by finding that carbon monoxide did not enter and leave the splenic blood so rapidly as it did the blood of the animal as a whole. They found also that the blood of the normal spleen is specially rich in red blood corpuscles. It is, however, very difficult to say how important this function is in man for the capsule of the human spleen is almost devoid of muscular tissue.

The blood is driven out when the organ contracts, the endothelium of the spleen pulp being continuous with that of the capillaries. By use of the plethysmograph Schafer and Moore demonstrated that it undergoes spontaneous rhythmical contractions which have presumably the function of changing the splenic contents from time to time

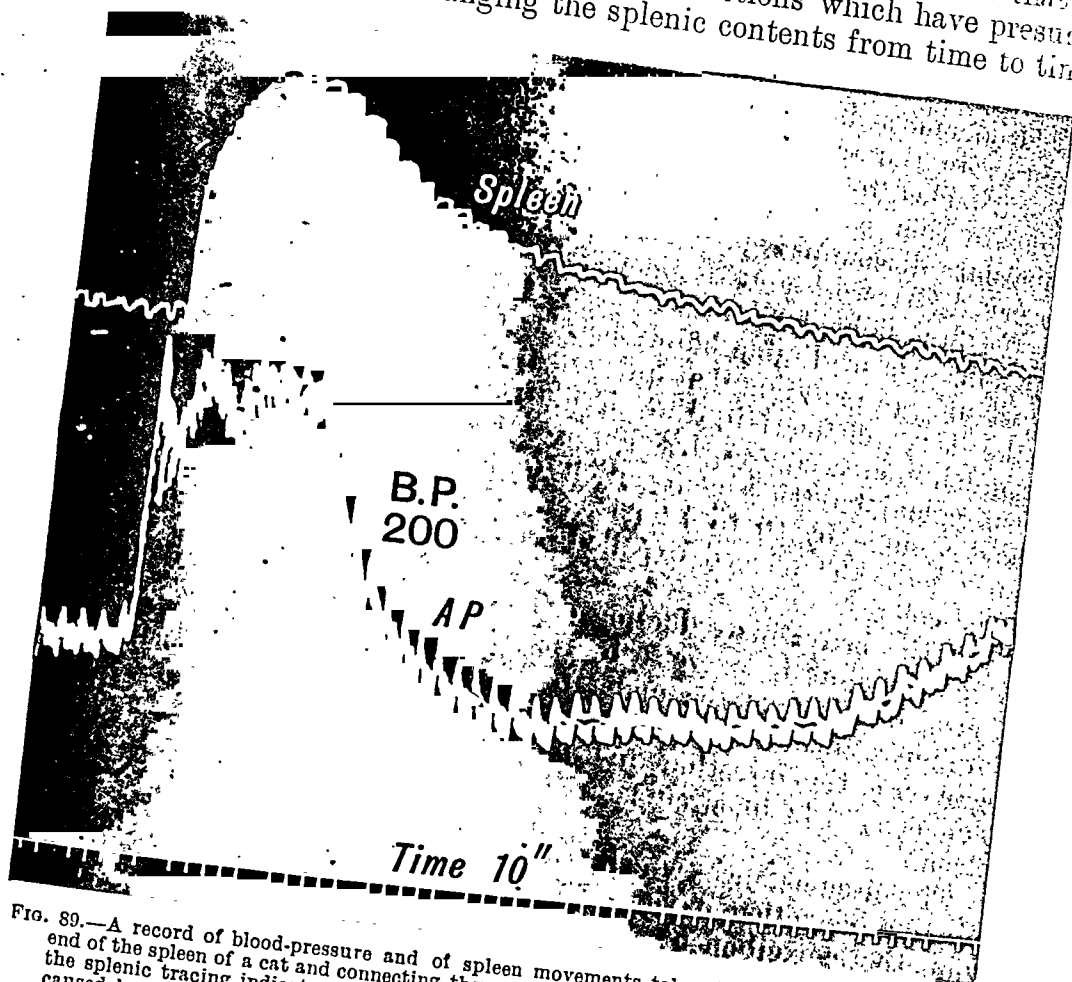


FIG. 89.—A record of blood-pressure and of spleen movements taken by tying threads to each end of the spleen of a cat and connecting them over pulleys to a lever. Upward movement in the splenic tracing indicates contraction. The record shows the contraction of the spleen caused by the intravenous injection of adrenaline. The vagi were intact and the rise of blood-pressure is not so large as it otherwise might have been. (McDowall.)

apart from that brought about by the blood flow. They found that it could be made to contract by a large number of different procedures. Thus, if the splenic nerves are cut, the organ relaxes; if, now, the peripheral ends are stimulated, it contracts. Apparently it is controlled by the vasomotor centre, since it contracts when the centre is stimulated by accumulation of carbon dioxide or by sensory stimulation, or when any part of the efferent pathway from the centre to the spleen, *e.g.* the spinal cord, certain anterior nerve-roots and splanchnic nerves, is stimulated. In exercise also when

the vasomotor centre and sympathetic nervous system generally are active the spleen is markedly reduced in size, as Barcroft has recently shown in the dog, by bringing the organ permanently to the surface, so that it may be observed under varying conditions.

A striking fact regarding the spleen is the surprising speed with which it may contract or relax (fig. 89, p. 183).

Other most ingenious methods have been used to observe its changes in the animal. For example, clips opaque to X-rays have been attached to its margins (McSwiney and Spurrell). It becomes fixed in this position, epithelium rapidly grows over it and no apparent discomfort is caused. Its contractions can then be observed (Barcroft and Stephens; Hargis and Mann).

At first sight it might seem that the amount of blood stored by the spleen is negligible but it has been shown by Daly on a closed heart-lung preparation that quite small quantities of blood, *e.g.* 30 c.c., make large changes in the circulation rate as the cardiac output is much increased, *e.g.* by 500 c.c. per minute. Actually it has been calculated that contraction of the spleen can increase the blood volume by 10 to 12 per cent. and the blood count by about 5 per cent. The blood expelled from the spleen is specially rich in red cells.

In the body this reduction of spleen capacity is detracted from to some extent in exercise by the increased capacity of the active tissues, but it must be understood that the power of acting as a storehouse for blood is probably shared by a number of abdominal organs, *e.g.* the intestine and liver. For example, the exteriorised colon constricts in circumstances similar to those which affect the spleen.

The circumstances which cause constriction in the unanæsthetised animal are emotion, oxygen-want and conditions which cause general sympathetic excitement.

It seems probable that in some of the lower animals the spleen is of more importance as a blood-depôt than in man. In the cat it may contain a third of the blood corpuscles in the body and about one-sixth of the total blood volume. In man the relative amount is much less and the spleen is much less muscular. It can be removed without producing any harmful effect.

Other Functions of the Spleen.

The presence of the Malpighian corpuscles with large nucleated cells and of so many white blood corpuscles in different stages of formation and its rhythmical contractions suggest, however, that in addition to being a blood depôt it probably has functions in regard to the quality of the blood. It would appear that a given quantity of

blood is held in the organ for a certain space of time and is thereby purified, or has added to it properties which are important. The spleen has been found to have the following additional functions:—

(1) The spleen, like the lymphatic glands, is engaged in *the formation of the white blood-corpuscles*, for the blood of the splenic vein contains an unusually large proportion of lymphocytes.

Removal of the spleen is not fatal; but after its removal there is an overgrowth of the lymphatic glands to make up for its absence.

(2) It plays an important part in some young animals in the formation of red blood-corpuscles, and in these when the spleen is removed the red bone-marrow hypertrophies.

(3) It also assists in the destruction of effete red blood-corpuscles and is therefore rich in lipides—cholesterol and lecithin—and in iron, of which it may be considered a storehouse. In most animals the organ is particularly rich in reticulo-endothelial cells, which as we shall see later have a particular function in ridding the blood of general debris.

(4) The spleen participates in nitrogenous metabolism, especially in the formation of uric acid (see Purine Metabolism).

These functions do not appear to be particularly important in normal persons, for, as we have seen, the spleen may be removed without any apparent harm to the subject. In disease, *e.g.* malaria, in which it helps to deal with the parasites, these functions of the spleen become grossly deranged, and instead of being a comparatively insignificant organ, it may become enormous.

HæmolympH Glands.

The existence of glands which partake of the nature both of the spleen and of lymphatic glands, has long been known. They have been fully investigated by Lewis. He finds them in most mammals, and they can be readily distinguished from ordinary lymphatic glands by their red colour. He distinguishes (1) *hæmal glands*, which are characterised by the fact that the sinuses contain blood only; the spleen is in fact a large hæmal gland; and (2) *hæmal lymphatic glands*, in which the sinuses are filled with a mixture of blood and lymph.

The Control of the Blood Depôts, including the Spleen.—It now seems probable that the blood depôts are controlled primarily by the depressor reflexes from the carotid sinus and the arch of the aorta. When blood is needed for any purpose, *e.g.* for muscular exercise, these reflexes are reduced with the result that the depôts

constrict and their store is thrown into active circulation. This reduction takes place primarily as a result of mental activity and produces (like a sponge being squeezed) an increased flow of blood to the heart. This in turn is responsible for the marked increase in systolic pressure which occurs in mental excitement. There is also splenic contraction as in hæmorrhage (see p. 174).

The evidence for the control of the blood depôts by the depressor reflexes is circumstantial. It has been found experimentally that the depôts dilate when the afferent paths of the reflex arcs are stimulated (*e.g.* the central end of the aortic depressor nerve) while inversely they contract if the reflexes are reduced (*e.g.* the carotid sinus impulses by occluding the common carotid artery). The probability that the depôts constrict during exercise and in mental activity is suggested by the marked increased output of the heart, associated with an increased systolic pressure without a corresponding increase in diastolic pressure. This is confirmed by observations on the exteriorised spleen already referred to. It is known, too, that the effect of the vagus on the heart is reduced in exercise, and that vagus activity depends on the activity of the depressor reflexes. Experimentally, all procedures which reduce the action of the vagus also reduce the activity of vascular components of the depressor reflexes (see p. 166) *e.g.* a rise of venous pressure and the injection of adrenaline. The rise of blood-pressure and increased heart rate in exercise in spite of the depressor reflexes suggest that these reflexes are reduced in such circumstances.

The Relationship of the Blood Depôts to the Tissue Fluid.—It has been emphasised by Cannon that in addition to calling on the blood depôts the body normally may call also on the tissue fluid in cases of emergency such as hæmorrhage. He considers the subcutaneous tissue as a specially valuable inundation area.

CHAPTER XVI

THE LYMPHATIC SYSTEM

As the blood circulates through the capillaries, some of its liquid constituents filter through the thin walls of these vessels, carrying nutriment and oxygen to the tissue cells. This exudation is called *tissue fluid*. In the tissues it has added to it the products of metabolic activity, notably water and carbon dioxide. Some of the tissue fluid finds its way back to the venous end of the capillaries, but most is collected in the lymph channels, which converge to the thoracic duct—the main lymphatic vessel—and thus once more enters the blood-stream at the junction of the left internal jugular and left subclavian vein (fig. 90). There is a smaller duct on the right side.

Lymph is therefore a fluid, which comes into much more intimate relationship with metabolic processes in the tissues than the blood.

Lymphatic Vessels.

The *lymph* is gathered up and carried back again to the blood by a system of vessels called *lymphatics*.*

The principal vessels of the lymphatic system are, in structure, like small thin-walled veins, provided with numerous valves which give them a beaded appearance. They commence in fine microscopic *lymph capillaries*, in the organs and tissues of the body. The fluid which they contain passes in one direction only from the fine branches to the trunk, and so to the large veins, on entering which it is mingled with the stream of blood. The lymphatic vessels of the intestinal canal are called *lacteals*, because during digestion (if the meal contains fat) the fluid contained in them resembles milk in appearance; and the *lymph* in the lacteals during the period of digestion is called *chyle*. Chyle is lymph containing finely divided fat-globules. We shall see presently that in some part of its course the lymph-stream passes through *lymphatic glands*.

Origin of Lymph Capillaries.—The lymphatic capillaries commence most commonly either (a) in closely-meshed networks (figs. 90 and 91), or (b) in irregular lacunar spaces, lined by endothelium,

* Some authors consider the tissue fluid and lymph to be separated by the wall of the lymph channels. (See below.)

Between the various structures of which the different organs are composed. These spaces, according to some authors, freely communicate with the cell spaces of the tissues; but some hold that no such communication exists, and that the lymphatics are everywhere closed at their origins like the lacteals which originate as blind dilated lymph spaces in the villi of the small intestine (see Small Intestine).

The structure of lymphatic capillaries is very similar to that of blood capillaries; their walls consist of a single layer of elongated endothelial cells with sinuous outline, which cohere along their edges to form a delicate membrane. They differ from blood capillaries mainly in their larger and very variable calibre, in the presence of

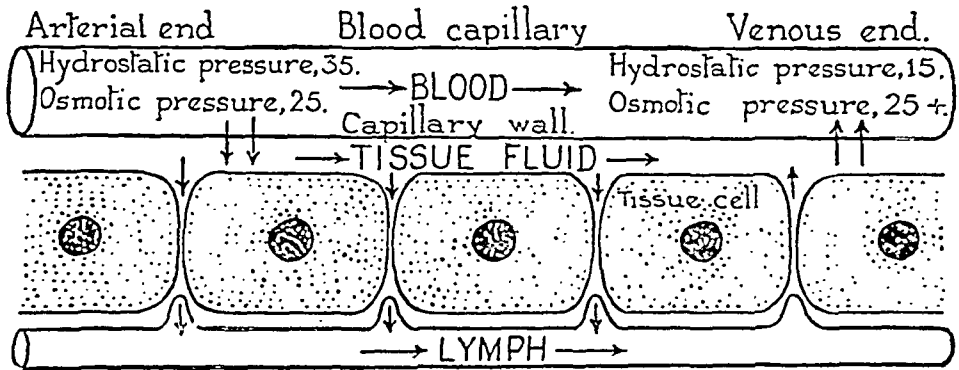


FIG. 90. (From Smout and McDowall.)

valves, and in the fact that when broken repair of their endothelium does not occur so rapidly.

In certain parts of the body, *stomata* exist, by which lymphatic capillaries directly communicate with parts formerly supposed to be closed cavities. They have been found in many serous membranes; a serous cavity thus forms a large lymph-sinus or widening out of the lymph-capillary system with which it directly communicates.

Lymphatic Glands.

Lymphatic glands are round or oval bodies varying in size from a hemp-seed to a bean, interposed on the course of the lymphatic vessels, and through which the lymph passes in its course to be discharged into the blood-vessels. They are found in great numbers in the mesentery, and along the great vessels of the abdomen, thorax, and neck; in the axilla and groin; a few in the popliteal space, and in the arm as far down as the elbow.

A lymphatic gland is covered externally by a capsule of connective tissue, generally containing some unstriated muscle. At the

inner side of the gland, the capsule sends inwards processes called *trabeculæ* in which the blood-vessels are contained, and these join with other processes prolonged from the inner surface of the part of the capsule covering the convex or outer part of the gland; they have a structure similar to that of the capsule, and, entering the gland from all sides and freely communicating, form a fibrous scaffolding. The interior of the gland is seen on section, even when examined with the naked eye, to be made up of two parts, an outer or *cortical*, which is light coloured,

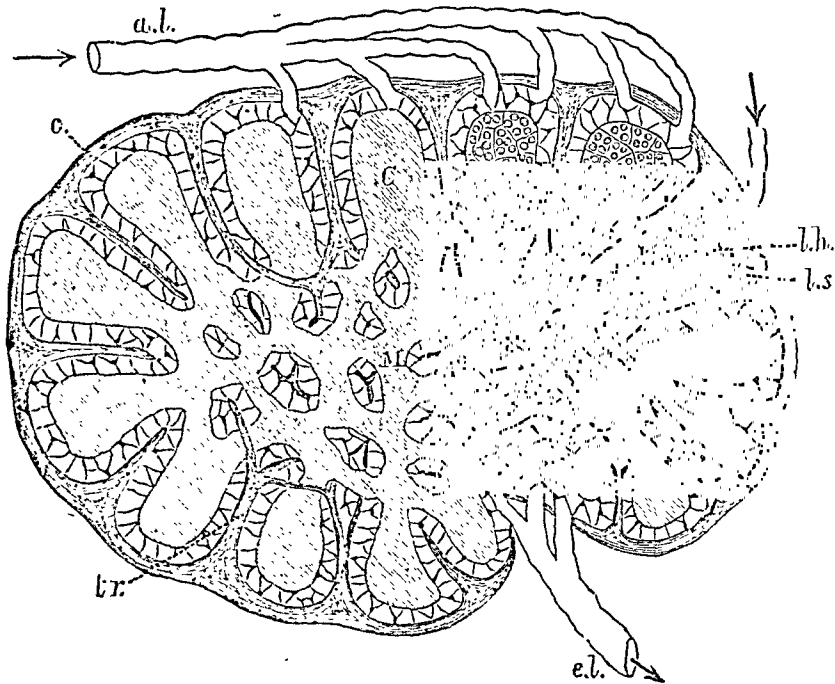


FIG. 91.—Diagrammatic section of lymphatic gland. a.l., Afferent; e.l., efferent lymphatics; C, cortical substance; l.h., lymphoid tissue; l.s., lymph-path; c., fibrous capsule sending trabeculæ, tr., into the substance of the gland. (Sharpey.)

and an inner or *medullary* portion of redder appearance (fig. 91). In the outer part, or cortex, of the gland the intervals between the trabeculæ are large and regular; they are termed *alveoli*; whilst in the more central or medullary part is a finer meshwork formed by an irregular anastomosis of the trabecular processes. Within the alveoli of the cortex, and in the meshwork formed by the trabeculæ in the medulla, is contained lymphoid tissue; this occupies the central part of each alveolus; but at the periphery, surrounding the central portion and immediately next the capsule and trabeculæ, is a more open meshwork of retiform tissue constituting the *lymph-path*, and containing but few lymph-corpuscles. At the inner part of the alveolus the central mass divides into two or more smaller rounded or cord-like masses which,

joining with those from the other alveoli, forms a much closer arrangement than in the cortex; spaces (fig. 92) are left within these anastomosing cords, in which are found portions of the trabecular meshwork and the continuation of the lymph-path.

The lymph enters the gland by several afferent vessels, which pierce the capsule and open into the lymph-path; at the same time they lay aside all their coats except the endothelial lining, which is continuous with the lining of the lymph-path. The *efferent* vessels begin in the medullary part of the gland, and are continuous with the lymph-path here as the afferent vessels are with the cortical portion.

The efferent vessels leave the gland at the *hilus*, and either at once, or very soon after, join together to form a single vessel.

Blood-vessels which enter and leave the gland at the hilus are freely distributed to the trabecular and lymphoid tissues.

The Formation of Tissue Fluid and Lymph.

The section on the passage of substances through membranes should be read by those unfamiliar with these subjects.

The formation of lymph may be investigated by putting a cannula into the thoracic duct and studying the amount and composition of the lymph under different conditions. Information may also be obtained by observing the circumstances in which fluid accumulates in the tissues and causes the swelling known as *œdema* or *dropsy*. This swelling is characterised by the fact that if present in the subcutaneous tissue as it commonly is in heart or kidney disease, it pits on pressure—that is, if the finger is pressed firmly into it a pit persists for some time.

The amount of fluid in the tissues may be increased in four ways, the first three of which also increase lymph-flow.

1. By increasing the capillary pressure.

This may be done by any obstruction to the venous flow from the part. This occurs in its commonest and severest forms in man when the general venous pressure rises as a result of cardiac failure, or if there is obstruction to the flow in the portal vein in disease of the liver. In the latter case the lymph accumulates in the abdominal cavity.

A mild degree of *œdema* in the feet may be produced simply by standing. If a subject stands quite still in a vessel of water the feet and legs can be observed to swell in about twenty minutes—by noting the rise in the level of the water.

These observations do not, however, completely prove that the *œdema* is the result of increased capillary pressure as slowed capillary flow also causes partial asphyxia of the part concerned which produces an increase of capillary permeability (see below) and increased

acidity of the tissues. It has been shown that acid colloids, *e.g.* proteins of tissues, tend to imbibe and retain water (Fischer).

The effects of increased capillary pressure may more conveniently be shown by injection of large quantities of fluid into the blood, especially if the fluid has an osmotic pressure less than that of the

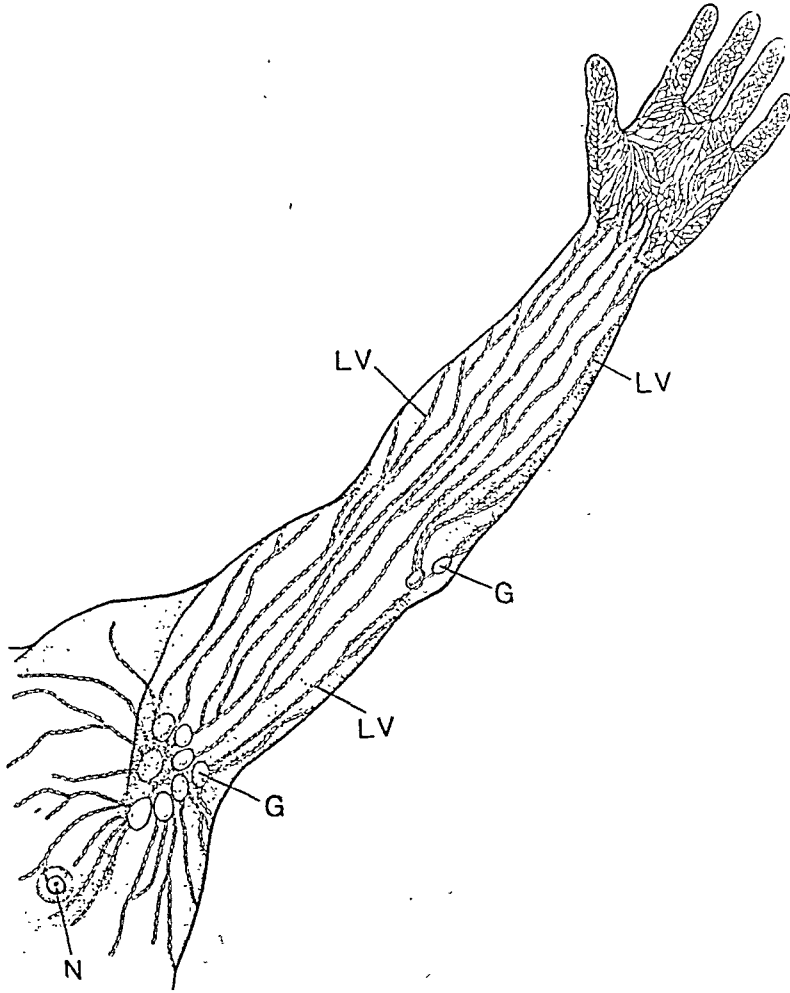


FIG. 92.—Illustration of the superficial lymphatics LV of the arm passing into glands (G) lying under the skin.

blood. If it has a higher osmotic pressure than the blood (concentrated sugar or salt) it attracts fluid from the tissues, but by increasing the blood volume and therefore the capillary pressure increases the flow of lymph from the thoracic duct. This is in part due to the fact that the kidney becomes incapable of excreting salts which retain water, but in many acute cases there is also an inability to excrete water.

2. By increasing the permeability of the capillary wall.

This occurs whenever the capillaries dilate, and may or may not be accompanied by tissue damage.

A simple dilatation occurs if the constrictor nerves to a part are cut. The increased flow of lymph caused by acetyl-choline or histamine may be produced in this way. Various other chemical substances may act similarly, such as peptone, leech extract and gin.

Heat as in burns, cold as in chilblain, and frostbite, mechanical irritation and inflammation cause tissue damage and at the same time liberate chemical substances which cause vasodilatation. In all such cases the fluid which escapes from the blood contains much more protein than normally. The fluid which accumulates in the pleural cavity, in pleurisy with effusion, or in the abdomen in peritonitis, therefore coagulates easily on being heated. In dropsy due to impaired venous return, it has been shown by Bolton that the diminished vitality of the capillary walls due to lack of oxygen is quite as important as the increased capillary pressure, since when, for example, the inferior vena cava is ligatured the onset of œdema is not immediate, but when once established continues for an appreciable time after the ligature has been removed.

Capillary permeability is greatly increased by a deficiency in blood calcium and is shown by the great benefits which commonly accrue from an increase in blood calcium in cases of chilblain and the like.

3. By increasing the osmotic pressure of the tissues. When the activity of the tissues increases, the products of metabolism raise the osmotic pressure of the tissue fluids because large molecules become broken down to smaller and consequently more water is attracted out of the blood. Here we may have the explanation of the stiffness which follows unaccustomed exercise. The muscles become swollen and painful as a result of increased tension, due to their taking up fluid from the blood. The best cure for such stiffness is therefore more exercise or massage to squeeze out the fluid.

4. By reducing the osmotic pressure of the blood. This may be done by the injection into the blood of dilute saline which very rapidly passes through the capillary walls into the tissue spaces.

An enormous local accumulation of fluid in the tissues may occur if the lymphatic channels become blocked. This occurs in the tropical disease known as filariasis in which the lymphatics become blocked by minute organisms. So large may the limbs become that the condition is known as elephantiasis.

From the experiments just described it is evident that the formation of lymph is, as originally pointed out by Ludwig, a physical phenomenon depending on the hydrostatic pressure in the

capillaries which, however, is, as pointed out by Starling, counteracted by the osmotic pressure of the blood which has an opposing effect and tends to suck fluid from the tissues into the blood.

The total osmotic pressure of the blood is almost 5000 mm. Hg., but by far the most of this is due to salts which are common to both the blood and the tissue fluid. It is the osmotic pressure of the proteins of the blood plasma which is of special importance in this connection, and this amounts to only about 25 mm. Hg. This is just overbalanced by the hydrostatic pressure in the capillaries of about 35 mm. Hg., the filtering force being about 10 mm. Hg.

Of more recent years these facts have been confirmed, especially by Drinker and his collaborators, and are supported by chemical studies of the composition of lymph.

At rest the capillary pressure is kept at a constant level by the constancy of the arterial pressure which, as we have seen, is maintained by various reflex mechanisms.

In exercise, however, a number of changes occur in the active tissue which must greatly increase the flow of lymph. These are:—

1. A rise of arterial pressure which raises the capillary pressure.
2. A dilatation of capillaries which become more permeable.
3. A breakdown of substances with large molecules, such as glucose, into substances which have many more and smaller molecules which increase the osmotic pressure of the tissues and cause them to imbibe water.

The Function of Tissue Fluid and Lymph.

We now get an idea of the function of the lymph-flow. When there is an increased capillary pressure and permeability there is an increased flow of fluid containing various nutritive substances in solution, while the greater flow of water towards the cells carries away with it the various products of metabolism. In various infections the lymph also carries bacteria from the tissues to the lymph glands; hence the benefit of keeping an infected region at rest and so preventing the lymph glands from being overcome by bacteria.

The formation of lymph is of interest in several other connections as it is the model on which many other body fluids, such as the aqueous humour of the eye, the fluid of the pericardium, the urine and secretion of glands are formed in the first instance, although the two latter are subsequently modified in composition.

The Phagocytic Function of Lymph.

Recent studies by Clark and Clark have shown that the lymphatics act as tissue scavengers. They sometimes grow out towards foreign

particles and eventually take them up. Things like blood corpuscles and fat globules pass readily into the lymphatics, sometimes directly from blood vessels. This is true especially in the liver.

The Lymph-Flow.

The flow of lymph may be readily shown if a suitable dye is injected into the foot of an anæsthetised animal, the hair of whose leg has been removed by a depilatory. The dye is seen to move slowly up the superficial lymphatics (Gilding). In severe infections of the hand the lymphatics of the arm of man may become inflamed and visible.

The flow depends essentially on the agencies which cause the formation of the lymph. Towards the point of its discharge into the veins the flow is assisted further. With the help of the valvular mechanism all occasional pressure on the exterior of the lymphatic and lacteal vessels propels the lymph onward; thus muscular and other external pressure accelerates the flow of the lymph as it does that of the blood in the veins. The action of the muscle-fibres of the small intestine, and the layer of unstriped muscle present in each intestinal villus, assists in propelling the chyle; in the small intestine of many animals the chyle has been seen moving with intermittent propulsions that correspond with the peristaltic movements of the intestine. For the general propulsion of the lymph and chyle, it is probable that, in addition to external pressure, some of the force is derived from the contractility of the vessels' own walls. The respiratory movements, also, favour the current of lymph through the thoracic duct as they do the current of blood in the thoracic veins.

Relation of Lymph and Blood.

The volume of blood in the body remains remarkably constant. If the amount is increased by injection of dilute saline (less than 0.9 per cent.), its specific gravity is at first lessened, but in a short time, often in a few minutes, it returns to the normal. The excess of fluid is got rid of in two ways: (1) by the kidneys, which secrete profusely; and (2) by the tissues, which become more watery in consequence. After the renal arteries are ligatured, and the kidney is consequently thrown out of action, the excess of water passes only into the tissues. More concentrated saline (about 0.9 per cent.) is retained longer until the salt is excreted by the kidney.

On the other hand, a deficiency of blood (for instance, after hæmorrhage) is soon remedied by a transfer of water from the tissues to the blood and a reduced production of lymph. This

may be looked upon as being brought about by the fall in the normal filtration pressure in the capillaries.

The Renewal of the Tissue Fluid.

The fluid of the tissues is of course of the same general composition as lymph although it may vary in different regions. During the exercise of a muscle or use of a tissue it is evident that the lymph flow is sufficient to renew this fluid but during rest the flow is very small. Evidence is accumulating (Landis) that there may be, as well as the lymph flow, a renewal of lymph by absorption. It is suggested that at the arterial end of the capillaries filtration is excessive, while at the venous end where the capillary pressure is lower by 20 mm. the increased osmotic pressure of the blood causes a withdrawal of fluid from the tissues.

Composition of Lymph.

From what has been said regarding its formation lymph is like blood-plasma in composition, but diluted so far as its protein constituents are concerned. This is due to the fact that proteins do not pass readily through membranes. The salts are similar to those of blood-plasma, and are present in about the same proportions. Chlorides, however, are more abundant in lymph than in blood. The waste products, such as carbonic acid and urea, are also more abundant.

Lymph is alkaline to litmus; its specific gravity is about 1015, and after it leaves the vessels it clots, forming a colourless coagulum of fibrin.

The degree of clotting depends on the amount of protein present. In the case of inflammatory lymphatic exudates as in pleurisy, the capillaries have become excessively permeable to protein. Liver lymph is richer in protein than lymph from the limbs.

When examined with the microscope the transparent lymph is found to contain corpuscles, which are called *lymphocytes*; these are cells with large nuclei and comparatively little protoplasm. They pass with the lymph into the blood, and constitute there one of the varieties of colourless blood corpuscles. They are added to the lymph wherever it passes through lymphoid tissue, *e.g.* lymphatic glands, tonsils, etc.

The Reservoir Function of the Tissue Spaces.

As has been indicated above, the fluid in the tissue spaces is very mobile and depends largely on the capillary pressure and the

osmotic pressure of the blood. When the capillary pressure falls, as in hæmorrhage, more fluid returns to the blood. This occurs too if the osmotic pressure of the blood is raised by loss of fluid in sweating or severe diarrhœa.

If the osmotic pressure is lowered by the intake of fluid, the tissue fluid, especially of the liver, skin and muscles, is increased.

It must be realised that most of the factors which affect the formation of tissue fluid influence the production of many other body fluids in the same way, *e.g.* the formation of urine, sweat, digestive secretions. All are influenced by the osmotic pressure and the hydrostatic pressure of the blood in opposite directions. (See Osmotic Pressure.)

REFERENCES.—Starling, Drinker, Landis.

CHAPTER XVII

RESPIRATION

THE term respiration in its wide sense includes all the processes and mechanisms by which the tissues of the body take up oxygen and get rid of carbon dioxide. The tissues are brought into relationship with the outside world indirectly by means of the blood which transports the gases, and in order to effect the exchange of gases rapidly the blood is spread out in a very thin but extensive layer, where it comes almost immediately into contact with the air, being separated only by a thin membrane. In order to provide the large area needed there have been evolved in many animals two specialised organs, lungs, in which the air is changed periodically by the mechanism of breathing. In fishes, the gills in contact with the water have a similar function. It is to be understood that the lungs are not in any manner the seat of any special combustion processes. Those processes take place in the tissues themselves.

The Respiratory Apparatus.

The respiratory apparatus consists of a pair of lungs and the air-passages which lead to them.

The *Lungs* are contained in the chest or thorax, which is a closed cavity having no communication with the outside except the trachea or windpipe.

The *Larynx* is at the upper end of the trachea, and will be described in connection with the voice.

The Trachea and Bronchi.—The trachea is essentially a tube of fibro-elastic membrane, within the layers of which is embedded a series of cartilaginous rings. These rings which maintain the patency of the windpipe extend only around the front and sides of the trachea (about two-thirds of its circumference) and are deficient behind; the interval between their posterior extremities is bridged over by a continuation of the fibrous membrane in which they are enclosed and by a layer of unstriped muscle.

The two bronchi into which the trachea divides have a similar structure, but there is a distinct layer of circular muscle which

becomes still more evident in the **bronchioles** into which the bronchi ultimately divide; indeed, the bronchioles are composed chiefly of a fibro-elastic membrane together with this circular muscle.

The whole bronchial tree is lined by ciliated epithelium which wafts upwards the secretion produced by mucous glands which open into the lumen, together with minute particles which may be inhaled. It is this secretion which forms the phlegm which becomes so excessive in bronchitis, while it is the contraction of the bronchial muscle which causes the tightness in the chest when the bronchioles are constricted, as in asthma. This is usually aggravated by the congestion of the mucous membrane. The bronchial muscle is kept in a state of tone by the vagus nerves and contracts rather surprisingly at the commencement of expiration—a fact which makes the removal of foreign bodies, accidentally taken in, very difficult. The muscle is dilated by sympathetic stimulants, such as adrenaline.

The Lungs and Pleuræ.—Each lung is enveloped by a serous membrane—the *pleura*, one layer of which adheres closely to its surface, and provides it with its smooth and slippery covering, while the other adheres to the inner surface of the chest-wall. The continuity of the two layers at the base of the lungs forms a closed sac, which the lungs fill completely. There is no actual space. The pleura which covers the lung (*visceral* layer) and that which lines the inner surface of the chest (*parietal* layer) are, in health, everywhere in very close apposition, being held together by a film of water which at body temperature can resist a pull of 3600 mm. Hg. (Burns). This film ensures the lungs gliding easily, in their expansion and retraction, on the inner surface of the parietal layer, which lines the chest-wall.

If, however, an opening is made so as to permit air or fluid to enter the pleural sac, the lung, in virtue of its elasticity, recoils, and a considerable space is left between it and the chest-wall. On the admission of air into the pleural sac the film of fluid is broken and atmospheric pressure bears alike on the inner and outer surfaces of the lung, and its elastic recoil is no longer prevented.

Each lung is partially subdivided into separate portions called *lobes*; the right lung into three lobes, and the left into two. Each of these lobes, again, is composed of a large number of minute parts, called *lobules*.

On entering a lobule, the small bronchial tube divides and subdivides (fig. 93); its walls at the same time become thinner and thinner, until at length they are formed only of a thin membrane of areolar, muscular, and elastic tissue, lined by a layer of pavement epithelium not provided with cilia. Eventually the muscle tissue disappears and the walls become pouched-out irregularly into small

saccular dilatations, called alveoli (see fig. 93). The funnel-shaped terminal branch of the bronchial tube, with its group of alveoli, is called an *infundibulum*. The alveoli are of various forms, according to the mutual pressure to which they are subject; their walls are nearly in contact, and they vary from 0.5 to 0.3 mm. in diameter. Their walls are formed of fine membrane, like those of the alveolar ducts and

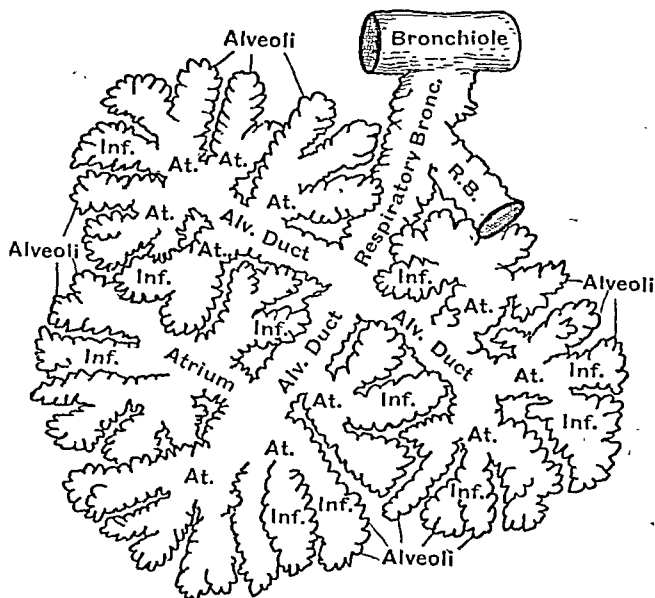


FIG. 93.—Diagram to show the general arrangement in a piece of lung.
(Modified from Miller.)

atria. They are lined by a layer of pavement epithelium (fig. 94). Outside the alveoli a network of pulmonary capillaries is spread out so densely (fig. 46, p. 93) that the interspaces or meshes are even narrower than the vessels. Between the air in the lungs and the blood in these vessels nothing intervenes but the thin-walls of the alveoli and of the capillaries; and the exposure of the blood to the air is the more complete, because the folds of membrane between contiguous alveoli, and often the spaces between the walls of each, contain only a single layer of capillaries, both sides of which are thus at once exposed to the air.

Blood-supply.—The lungs receive blood from two sources: (a) the pulmonary artery, (b) the bronchial arteries. The former conveys *venous* blood to the lungs to be *arterialised*. The branches of the bronchial arteries convey arterial blood from the aorta for the nutrition of the walls of the bronchi, vessels, interlobular connective tissue, etc.; the blood of the bronchial vessels is returned chiefly through the bronchial and partly through the pulmonary veins.

The Respiratory Mechanism.

Respiration consists of the alternate expansion and contraction of the thorax, by means of which air is drawn into or expelled from the lungs. These acts are called *Inspiration* and *Expiration* respectively.

For inspiration a movement of the side-walls and floor of the chest takes place, so that the capacity of the interior is enlarged. By such increase of capacity there will be a diminution of the

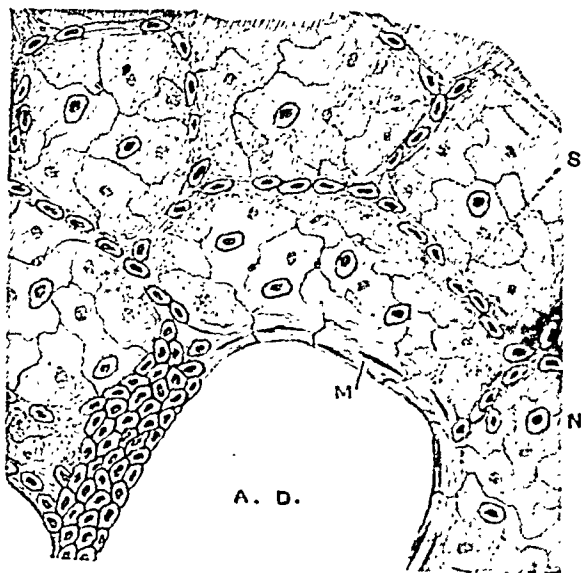


FIG. 94.—Section of lung stained with silver nitrate. A. D., alveolar duct or intercellular passage; S, alveolar septa; N, alveoli or air-sacs, lined with large flat cells, with some smaller polyhedral cells; M, plain muscle-fibres surrounding the alveolar duct. (Klein and Noble Smith.)

pressure of the air in the lungs, and a fresh quantity will enter through the trachea to equalise the pressure on the inside and outside of the chest.

For expiration the opposite movement diminishes the capacity of the chest; the pressure in the interior will be thus increased, and air will be expelled, until the pressures within and without the chest are again equal. In both cases the air passes through the trachea, there being no other communication with the exterior of the body; and the lung remains, under all conditions, closely in contact with the walls and floor of the chest. The movements of the lungs are therefore passive, not active, and depend on the changes of shape of the closed cavity in which they are contained. A perforation of the chest-wall would mean that the lung on that side would no longer be of use; a similar injury on the other side (double pneumothorax) would cause death. If the two layers of the pleura were adherent, those portions of the lung would be expanded most where the move-

ments of the chest are greatest. The existence of the two separate layers prevents this, and thus the lung is equally expanded throughout.

Keith believes that the expansion of the lung during inspiration does not occur simultaneously at every point but resembles rather the opening of a Japanese fan. First the anterior borders and the part in contact with the diaphragm expand followed successively by the apex, vertebral border, and region of the root.

Inspiration.—This is a muscular act; the inspiratory muscles increase the size of the chest-cavity in all its diameters.

The *vertical diameter* is increased by the contraction and consequent descent of the diaphragm; at rest, the diaphragm is dome-shaped with the convexity upwards; the central tendon forms a slight depression in the middle of this dome. On contraction the muscle-fibres shorten, and so the convexity of the double dome is lessened. The central tendon is drawn down a certain distance, but the chief movement is at the sides. For the effective action of this muscle, its attachment to the lower ribs is kept fixed by the contraction of the *quadratus lumborum*. The diaphragm is supplied by the *phrenic* nerves, which arise chiefly from the 4th cervical segment of the spinal cord.

The increase in the *lateral* and *antero-posterior diameters* of the chest is effected by the raising of the ribs, the upper ones being fixed by the *scaleni*. The greater number of the ribs is attached very obliquely to the spine or vertebral column, and sternum.

The elevation of the ribs takes place both in front and at the sides—the hinder ends being prevented from performing any upward movement by their attachment to the spine. The movement of the front extremities of the ribs is of necessity accompanied by an upward and forward movement of the sternum to which they are attached, the movement being greater at its lower than at its upper end.

The muscles by which the ribs are raised, in *ordinary* quiet inspiration, are the *external intercostals*, and that portion of the *internal intercostals* which is situated between the costal cartilages; and these are assisted by the *levator costarum*, and the *serratus posterior superior*.

In *extraordinary* or forced inspiration, additional muscles are pressed into service, such as the *sternomastoid*, the *serratus anterior*, the *pectorales*, and the *trapezius*. Laryngeal and face muscles also come into play.

The expansion of the chest in inspiration presents some peculiarities in different persons. In young children it is effected chiefly by the diaphragm. The movement of the abdominal walls being here more manifest than that of any other part, it is usual to call this the *abdominal* type of respiration. In men, together with the descent of the diaphragm and the pushing forward of the front wall of the abdomen, the chest and the sternum are subject to a wide movement

in inspiration (*inferior costal type*). In women the movement appears less extensive in the lower, and more so in the upper, part of the chest (*superior costal type*).*

Expiration.—From the enlargement produced in inspiration, the chest and lungs return, in ordinary tranquil expiration, by their elasticity to their previous condition; the force employed by the inspiratory muscles in distending the chest and overcoming the elastic resistance of the lungs and chest-walls, is returned as an expiratory effort when the muscles are relaxed. This elastic recoil of the chest and lungs is sufficient, in ordinary quiet breathing, to expel air from the lungs in the intervals of inspiration, and no muscular power is required. In all voluntary expiratory efforts, however, as in speaking, singing, blowing, and the like, and in many involuntary actions also, as sneezing, coughing, etc., something more than merely passive elastic power is necessary, and the proper expiratory muscles are brought into action. The chief of these are the abdominal muscles, which, by pressing on the viscera of the abdomen, push up the floor of the chest formed by the diaphragm, and by thus making pressure on the lungs, expel air from them through the trachea and larynx. All muscles, however, which depress the ribs, must act also as muscles of expiration, and we must conclude that the abdominal muscles are assisted in their action by the interosseous part of the *internal intercostals*, the *triangularis sterni*, and perhaps the *serratus posterior inferior*. When by the efforts of the expiratory muscles, the chest has been squeezed to less than its average size, it again, on relaxation of the muscles, returns to the normal dimensions by virtue of its elasticity. The construction of the chest-walls, therefore, admirably adapts them for recoiling against and resisting undue contraction as well as undue dilatation.

At the commencement of the expiratory act there is a closure of the larynx which can be readily recorded. Expiration is therefore against resistance.

Graphic Record of Respiratory Movements.

Among numerous methods which have been described for recording the respiratory movements the simplest in the human subject, especially if he be a patient in bed, is to fasten a bandage loosely round the chest. Between the bandage and the chest-wall a flexible hollow rubber ball is placed. This ball or a tambour communicates by a rubber tube with a recording tambour. All such appliances are called *Stethographs*.

The tambour which was first introduced by Marey is shown in fig. 95.

* Inspiration is easier when sitting or standing because the return of blood to the heart is reduced (Burns). This is important clinically.

It is possible to record the diaphragmatic movements in animals by the insertion of an elastic bag connected with a tambour into the abdomen below the diaphragm, by the insertion of needles into

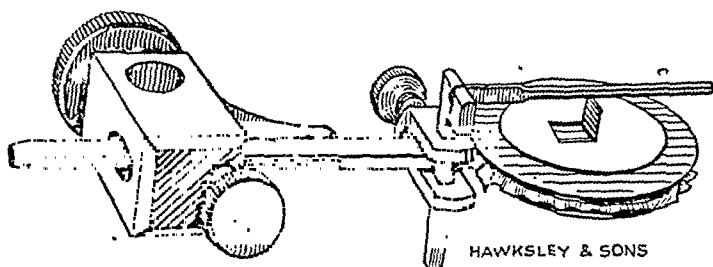


FIG. 95.—A modification of Marey's tambour to which the movement of a column of air is conducted by a tube from another tambour or balloon. Various arrangements are seen by which the writing lever may have its excursions modified or may be adjusted to the writing surface—a smoked paper on a revolving cylinder. (McDowall, by permission of Messrs Hawksley.)

different parts of its structure, or by recording the contraction of isolated strips of the diaphragm. Such a strip attached in the rabbit to the xiphisternal cartilage may be detached, and attached

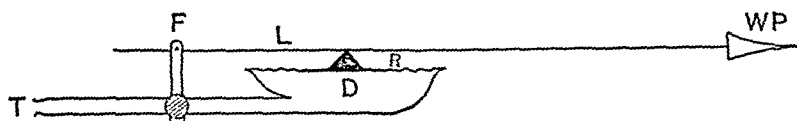


FIG. 96.—Diagrams of a recording tambour (after Marey). D, Drum covered with thin rubber R, and carrying a lever L with a fulcrum at F and a writing point WP. The tube T connects with the receiving tambour.

by a thread to a recording lever; this strip serves as a sample of the diaphragm.

Such methods, however, merely measure the rate of breathing and give a rough idea of its depth. The actual quantity of air

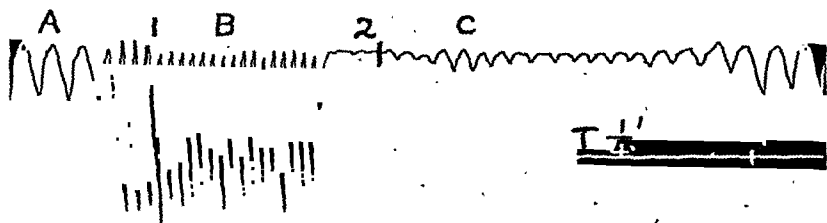


FIG. 97.—Record showing normal respiration at A, the effect of over-ventilation at B, the gradual return to normal at C during respiration is seen. Pieces of tracing were cut out at 1 and at 2 to (Wilkinson.)

which enters and leaves the lungs is measured by a modified gasometer (*spirometer*) (fig. 98) into which the subject breathes.

The variations of intrapleural pressure may be recorded by the introduction of a cannula into the pleural cavity, which is connected with a water manometer.

The act of inspiring air, especially in women and children, is a

little shorter than that of expelling it, and there is commonly a very slight pause between the end of expiration and the beginning of the next inspiration.

If the ear is placed in contact with the wall of the chest, or is separated from it only by a good conductor of sound or stethoscope, a *respiratory murmur* or breath sound is heard chiefly during inspiration. This sound varies somewhat in different parts—being loudest or coarsest in the neighbourhood of the trachea and large bronchi (tracheal and bronchial breathing), and fading off into a faint sighing as the ear is placed at a distance from these (vesicular breathing). It is best heard in children, and in them a

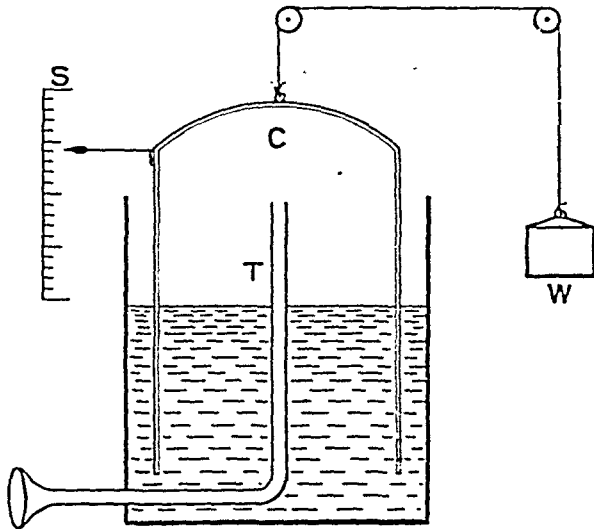


FIG. 98.—The Hutchinson spirometer. The weight W is to balance the weight of the cylinder C.*

more marked murmur is heard in expiration. The cause of the vesicular murmur has received various explanations; but most observers hold that the sound is produced by the air passing through the glottis and larger tubes, and that this sound is modified in its conduction through the substance of the lung. The alterations in the normal breath sounds, and the various additions to them that occur in different diseased conditions, can be properly studied only at the bedside.

During the action of the muscles which directly draw air into the chest, those which guard the opening through which it enters are not passive. In hurried breathing the instinctive dilatation of the nostrils is well seen, although under ordinary conditions it may not be noticeable. In many people the *rima glottidis*, or interval between the true vocal cords of the larynx, is slightly dilated at

* In the Benedict-Roth spirometer a writer is attached to the weight and writes from below upwards as the cylinder empties.

each inspiration for the more ready passage of air, and becomes smaller at each expiration; its condition, therefore, corresponds during respiration with that of the walls of the chest. There is a further likeness between the two acts in that, in ordinary circumstances, the dilatation of the rima glottidis is a muscular act and its narrowing chiefly an elastic recoil.

Quantities of Air Breathed.—Measurements of these quantities are made by means of the spirometer. The apparatus is illustrated and is seen to consist of a light metal bell (C), which is balanced by a counterweight (W), and which can move freely in a water-container. The subject breathes into the tube (T). Several modifications of this apparatus have been made, notably Krogh's recording spirometer and the Benedict-Roth apparatus, by which it is possible to take continuous records of the air breathed in and out.

Tidal air is the quantity which is habitually and almost uniformly changed in each act of breathing. In a healthy adult man it averages about 500 c.c., or rather more than 30 cubic inches (Haldane). This will be expanded at body temperature to 600 c.c. This amount of air is not sufficient to fill the lungs. Haldane gives the capacity of the upper air-passages and bronchial tubes as 200 c.c., and therefore about a third of the tidal air is required to fill this *dead space*.

Complemental air is the quantity over and above the tidal air which can be drawn into the lungs in the deepest inspiration; its amount averages 100 cubic inches (1600 c.c.).

Reserve or Supplemental Air.—After an ordinary expiration, such as that which expels the tidal air, a further quantity of air, about 100 cubic inches (1600 c.c.) can be expelled by a forcible deep expiration. This is termed *reserve* or *supplemental air*. The last portion of the air thus expelled will consist of *alveolar air*.

These relationships are seen in fig. 99, p. 206.

Vital Capacity.—The vital capacity of the chest is indicated by the quantity of air which a person can expel from his lungs by a forcible expiration after the deepest inspiration possible. The Royal Air Force requires a vital capacity of at least 3800 c.c. but figures up to 10,000 have been known. It is the sum of the complemental, tidal, and supplemental air. This determination is commonly made in medical practice, since in diseased states, *e.g.* cardiac disease, the vital capacity may be much reduced.

The vital capacity is also reduced at high altitudes and in exercise. Verzár, who has studied this problem, has found that any form of oxygen-want increases the total volume of the lungs and he concludes that this results in a greater lung surface being available to the blood and that the increased volume is the result of an increase in the residual air.

The expired air is a mixture of air from the trachea, bronchi, and lungs. It is in composition intermediate between the outside and the alveolar air.

Residual air.—The existence of this air was suggested by the fact that even when the lungs are quite collapsed and removed from the body they float and air may be squeezed out, while the amount has been found by finding the total capacity of the lungs. This is done by filling a spirometer with a known volume of an inert gas such as hydrogen. After two forced respirations the

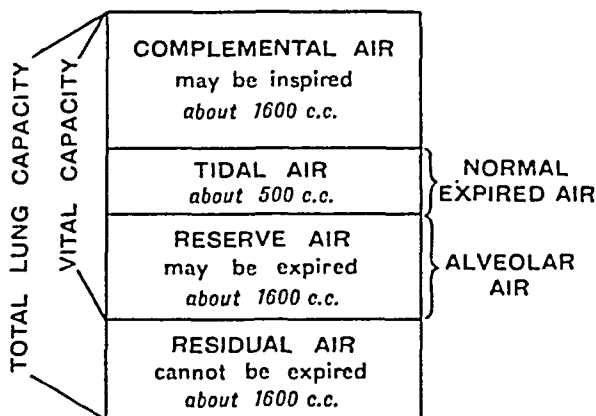


FIG. 92.

dilution of the hydrogen in the spirometer is obtained and it is found that this is greater by about 1600 c.c. than can be accounted for by the vital capacity.

The number of respirations in a healthy adult person usually ranges from 14 to 18 per minute. It is greater in infancy and childhood. It also varies much according to different circumstances, such as exercise or rest, health or disease, etc. Generally the larger the amount of the tidal air the slower the respirations. A centre forward of the Heart of Midlothian football team had a tidal air of 3 litres and only needed to breathe four times per minute. Even in severe exercise his rate was nine per minute.

The Respiratory Quality of the Air.—From what has been said it is evident that the air in contact with the blood is that of the alveoli. From the following table its composition may be compared with that of the atmosphere and of the expired tidal air. It is to be understood, however, that these figures may vary in different circumstances, but the *averages* obtained from normal individuals at rest are sufficiently important in an understanding of respiration to be committed to memory.

Per Cent. by Volume.	Atmosphere.	Expired Air.	Alveolar Air.
Oxygen . . .	20.96	16.0	13-14
Carbon dioxide . .	0.04	4.4	5-6
Nitrogen . . .	79.0	79.6	80-82

The relation of these values to tidal air, etc., is indicated by fig. 99, and especially by fig. 110, p. 227.

The expired and alveolar airs are saturated with water vapour at body temperature.

METHODS OF INVESTIGATION.

Although these methods were originally used in the purely scientific investigation of respiration, their use has now been extended to the study of diseased conditions, and a knowledge of their use has become essential to medical students.

The Collection of Alveolar Air.

Haldane and Priestley introduced a simple method of collecting alveolar air which has the advantage of being applicable to man. It consists essentially of collecting the air expired at the end of a

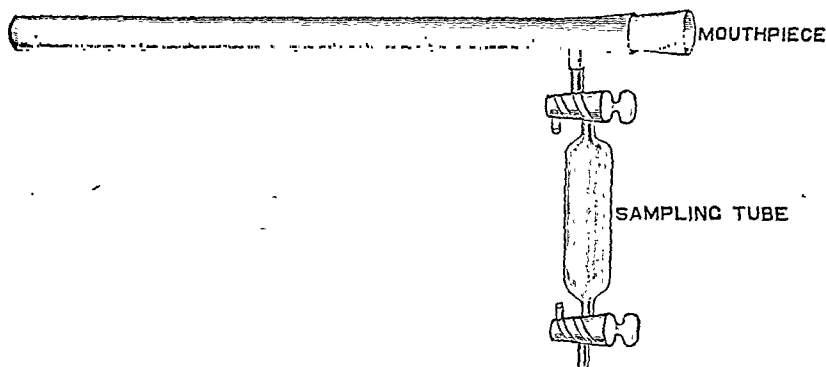


FIG. 100.—Apparatus for obtaining alveolar air.

deep expiration. A piece of rubber tubing is taken about 1 inch in diameter and about 4 feet long. A mouthpiece is fitted into one end, and 2 inches from the mouthpiece is a smaller rubber tube through which samples may be withdrawn into a sampling tube (fig. 100). The latter is made of glass and has a tap at each end. Before it is used it is evacuated (conveniently by filling it with mercury and allowing it to run out). The subject of the experiment breathes normally through the tube for a time until he becomes accustomed to it, and then, at the end of a normal inspiration,* he expires quickly and very deeply through the mouthpiece and instantly closes it with his tongue. A second experiment is then done, in which the subject expires deeply at the end of a normal

* This inspiration should not be through the tube.

expiration, and another sample is obtained. The mean result of the two analyses represents the composition of the alveolar air. Since the gaseous interchange between the blood and the alveolar air is going on continuously, it is evident that at the end of inspiration there will be a maximum percentage of oxygen, and a minimum percentage of carbonic acid; the converse obtains at the end of expiration.

On analysis the composition of alveolar air is found to be 13-14 per cent. of oxygen and 5 to 6 per cent. of carbon dioxide.

These percentages may, however, be caused to vary according to the ventilation in the lungs. If respiration is increased voluntarily the alveolar air becomes more like atmospheric air, *i.e.* the percentage of carbon dioxide falls. This occurs whenever the respiratory centre is stimulated by substances in the blood *other than carbon dioxide*, *e.g.* by voluntary over-ventilation or by acids such as those produced in diabetes. A fall of alveolar carbon dioxide is therefore of considerable diagnostic significance as (see Acid-Base Equilibrium) it indicates an attempt of the body to rid itself of excessive acid, as, for instance, in diabetes mellitus. Similarly, reduced respiration due to any cause except lack of CO_2 causes a rise in alveolar CO_2 .

The Collection of Expired Air.

In measuring the *total ventilation* (cubic centimetres of air passing in and out of the lungs per minute) it is usual to measure the volume of the air expired in a given time. This is not quite the same thing as the volume of the inspired air, because the CO_2 added to the air is a little less in volume than that of the oxygen which it replaces.

The subject, whose nose is clipped, breathes by the mouth through a tube in which there are suitable valves. By attaching a tube to the expiratory valve the expired air can be collected in a bag. The type of bag most frequently used for this purpose is that devised by Douglas of Oxford. The Douglas bag is made of canvas impregnated with rubber; its walls must be impervious to CO_2 , flexible, and not too heavy. It is fitted with a tap which can be turned quickly so that the duration of an experiment can be timed exactly. The sample collected is kept for subsequent measurement and analysis. The tubing used for connecting the face mask to the bag must have a very wide bore; even a small constriction adds greatly to the labour of respiration and causes respiratory fatigue.

The volume of the sample is obtained by passing the contents of the bag through a gas meter, and a side tube facilitates the collection of small samples for analysis. In this way (1) the total ventilation, (2) the oxygen in the expired air, and therefore the oxygen absorbed by the subject, (3) the CO_2 in the expired air,

and its output per minute, and (4) the respiratory quotient (the proportion of CO_2 given out to oxygen taken in) are obtained. These data are also needed in reference to work on nutrition, and

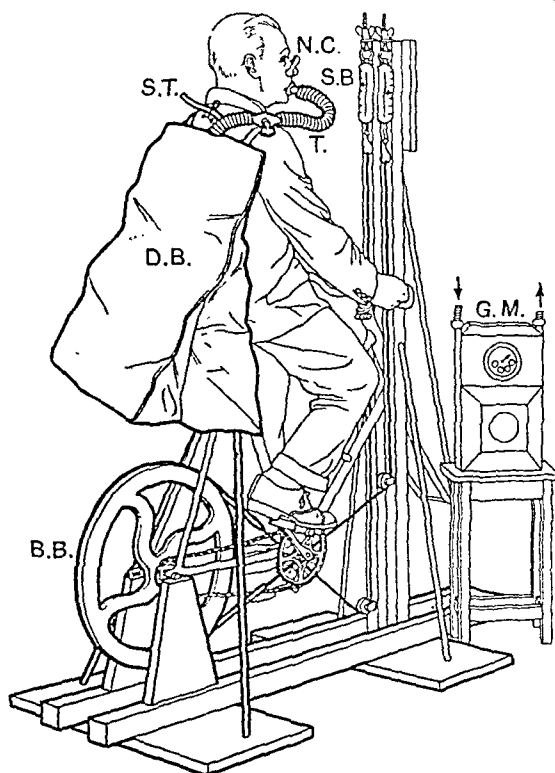


FIG. 101.—Douglas Bag and Bicycle Ergometer. D.B., Douglas bag strapped on back of subject and connected to his mouth by a wide corrugated tube with a tap opening to the outside; N.C., nose clip; S.T., rubber sampling tube with clip; B.B., band-brake attached by cords to spring-balances, S.B.; G.M., gas meter for measuring volume of air in bag.

may also be employed in calculating the quantity of blood circulating per minute.

On **analysis** the expired air is found to be between alveolar and the inspired air—*i.e.* to contain **16 per cent. oxygen** and **4·4 per cent. carbon dioxide**. The more efficient the ventilation the more like atmospheric air the expired air becomes. Over-ventilation, therefore, causes the percentage of oxygen to rise and that of the carbon dioxide to fall, and care must be taken to avoid this in collecting a sample by ensuring that the subject breathes naturally.

The Principles of Gas Analysis.

The gases one has to deal with, whether pumped off by the vacuum pump from the blood, obtained from the pulmonary alveoli, or from the atmosphere, are only three in number. The total gas

obtained is first measured, then the *carbon dioxide* is removed by caustic potash (KOH) and the gas that remains is measured; this consists of *oxygen* and *nitrogen*. The oxygen is removed by pyrogallic acid in KOH and the gas again measured; this is *nitrogen*.

The Haldane Gas Analysis Apparatus.

This is the classical apparatus for gas analysis, but many modifications in detail have been devised (fig. 102). J. S. Haldane (1860-

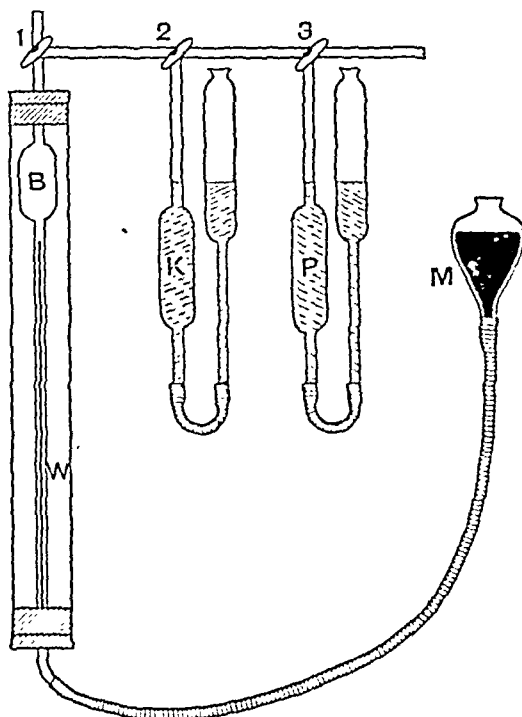


FIG. 102.—A simplified Haldane gas analysis apparatus.

1936) carried out most of his researches with Douglas and Priestley in Oxford.

In its simplest form it consists of a burette (B) surrounded by a water-jacket (W) to which there is connected, by means of rubber-tubing, a mercury reservoir. *After preliminary adjustments** a sample is drawn into the burette by lowering the mercury (M) which previously has been raised to fill the burette completely. When the air to be examined is in a sampling tube its place in the tube is taken by fluid from a reservoir attached by tubing to its lower end, the upper

* These adjustments include the exposure of all air in the apparatus to pyrogallol to ensure that only nitrogen is present.

end being attached to the analyser. The tap 1 is then closed and the sample measured (at atmospheric pressure, by levelling the surface of the mercury in the reservoir with that in the burette). The taps 1 and 2 are then turned so that the burette communicates with the bulb (K) containing 10 per cent. KOH, and the sample is driven over and drawn back from this bulb several times. The level in the bulb is brought back to zero by adjusting the level of the mercury reservoir. The tap 1 leading from the burette is now closed and the sample measured at atmospheric pressure as before. The decrease in the volume of the sample is a measure of the CO_2 absorbed. The sample is driven over until absorption is complete.

The procedure is repeated using tap 3, so that the gaseous sample enters the pyrogallol bulb (P) instead of the KOH and is continued until no further absorption occurs. This may take half an hour. The further diminution in volume indicates the amount of oxygen in the sample.

Before commencing the analysis the direction of the taps must be known. The taps must be turned to connect the bulbs with the atmosphere and the levels of the solutions in the bulbs are adjusted to zero. All CO_2 and oxygen must be removed from the tubes connecting the bulbs with the burettes by carrying out a preliminary analysis of room air. It is important also to emphasise that since the pyrogallol will absorb CO_2 as well as oxygen the carbon dioxide must be absorbed first.

Micro-gas analysis.—This is necessary when analysing the gases in a bubble of air as in determining the tension of gases in blood. The burette is replaced by a graduated tube of capillary bore into which KOH and pyrogallol are alternately sucked by various devices.

CHAPTER XVIII

RESPIRATION (*continued*)

The Gases of the Blood

BEFORE the student can study either the chemistry of respiration or its regulation, which is in part a chemical process, it is necessary that he should have an adequate conception of the fundamental laws which regulate the retention of oxygen and carbonic acid in the blood; and as the blood presents many complications, it will be best at the outset to consider the solution of gases in such a simple medium as water.

Solution of Gases in Water.

If water is shaken up with a gas, a certain definite amount of the gas will be dissolved in the water. Under the same conditions the same quantity of oxygen will always be dissolved. The temperature is important, but to simplify the following argument it will be assumed that the temperature remains constant, so that this factor may be neglected. The amount dissolved depends then on two factors, each of which can be measured. The first is the pressure of the gas to which the water is exposed when shaken; the second is the solubility of the gas in water. The solubilities of different gases differ very much; some (for instance, oxygen) are but slightly soluble in water, while others, such as carbonic acid, are very soluble.

If a cubic centimetre of water is introduced into a large air-tight bottle containing pure oxygen at atmospheric pressure, and another cubic centimetre of water is placed in a bottle containing pure carbonic acid at the same pressure, the former will dissolve 0.04 c.c. of oxygen, the latter 1 c.c. of carbonic acid. These figures represent the degrees to which the two gases are soluble in water in similar circumstances, and are called the *coefficients of solubility*. The coefficient of solubility of gas in a liquid is therefore the volume of gas which 1 c.c. of the liquid will dissolve at 760 mm. of mercury, that is, atmospheric pressure.

The quantity of gas which a liquid will dissolve depends not only on the solubility of the gas, but also on the pressure of the gas to which the liquid is exposed. Thus, in the instance given above, if the oxygen had been rarefied in the bottle until it exerted a pressure

of only one-fifth of an atmosphere, the water would have taken up not 0.04 c.c. of oxygen, but only one-fifth of that amount, 0.008 c.c. To take another example, 1 c.c. of water shaken up with pure nitrogen at 760 mm. pressure will dissolve 0.02 c.c.; but if the pressure is reduced to four-fifths of the atmospheric pressure, then the water will dissolve $0.02 \times \frac{4}{5} = 0.016$ c.c. If we represent the coefficient of solubility of a gas by K , the pressure of the gas to which the liquid is exposed by P' , and the atmospheric pressure by P ; then the quantity, Q , of the gas dissolved by 1 c.c. of the liquid may be obtained by the following formula—

$$Q = K \times \frac{P'}{P}.$$

Dalton-Henry Law.

What has been said above is as true of gases which are mixed together as of pure gases. For instance, we have seen that a cubic centimetre of water shaken up with oxygen at one-fifth of an atmosphere (152 mm. pressure) will absorb $0.04 \times \frac{1}{5} = 0.008$ c.c.; or if shaken with nitrogen at a pressure of four-fifths of an atmosphere, it will dissolve $0.02 \times \frac{4}{5} = 0.016$ c.c. If now a c.c. of water be shaken with air (a mixture of one part of oxygen to four of nitrogen), it will have absorbed 0.008 c.c. of oxygen and 0.016 c.c. of nitrogen. The fact may be summarised thus:—When two or more gases are mixed together, each of them produces the same pressure as if they separately occupied the entire space and the other gases were absent. The *total* pressure of the mixture is the sum of the *partial* pressures of the individual gases in the mixture.

Estimation of Blood Gases.

The classical method of obtaining gases from the blood has been that of "boiling off" the gases from the blood by creating a vacuum above it. The different patterns of air pump vary in different laboratories. For general use, however, the chemical methods are much more convenient.

Haldane's and Barcroft's Methods.—In both of these the oxygen is liberated from the blood by potassium ferricyanide, and subsequently the carbon dioxide by tartaric acid. The blood, oxalated to prevent clotting, is placed in a small chamber (A) beneath weak ammonia solution (to fix the free CO_2), and laked with saponin. Within the chamber is a small container of fresh saturated aqueous solution of potassium ferricyanide. The appliances differ in the methods of measuring the gas given off and in the shape of the chambers. In each there is a similar chamber in which a similar quantity of water

or blood may be placed as a control, with which the sample may be compared.

In the *Barcroft apparatus* (fig. 103) the gas given off drives a column of clove oil along a U-tube. The difference in the level of the oil in the two limbs is proportional to the amount of gas evolved.

In the *Haldane apparatus* (fig. 103) the amount of gas evolved is measured directly in the burette C, in which the fluid is driven down, the second small chamber (D) introducing an automatic correction for any expansion or contraction of gases in the apparatus due to accidental changes in temperature (E). This possibility is reduced by immersing the chambers in a bath of water at a constant temperature. The tubes T contain acidulated water containing a dye and bile salts to reduce surface tension.

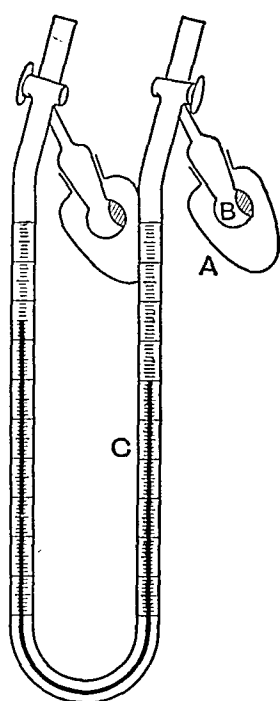
If the blood has been saturated the above gives the *oxygen capacity* of a sample. To obtain the *oxygen content* of a given blood, the sample is put in the chamber, great care being taken to prevent it from coming in contact with air. The chamber is now shaken and the diminution in the volume of the air in the burette indicates the amount taken up. This subtracted from the capacity gives the oxygen content.

When large quantities of blood are available, the older Dupré's apparatus may be used (see Urea Estimation), to which the letters used above also apply.

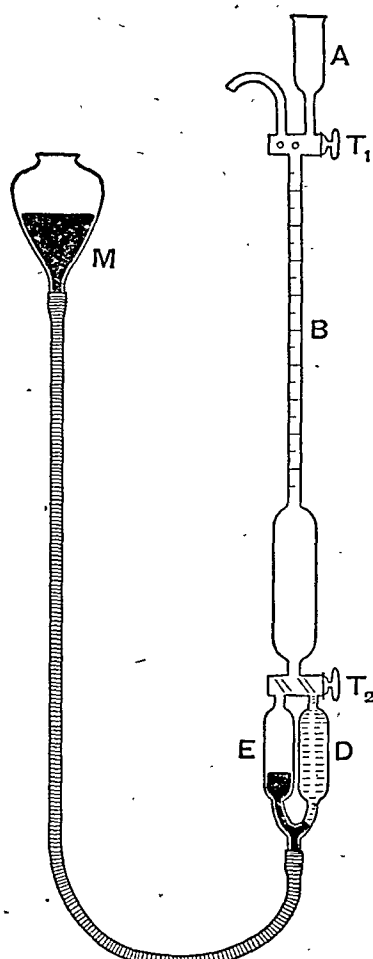
Estimation of the Carbon Dioxide Content or Combining Power of Blood.—This can be carried out on the same specimen as used in the estimation of the oxygen capacity. The stopper is removed from A, and B is replaced by another small tube containing an aqueous solution of tartaric acid.* The stopper is replaced, the fluids mixed, and the remainder of the estimation is carried out as described above for the oxygen capacity. A certain amount of carbon dioxide is lost during the process of oxygenation, and special methods, e.g. that of Van Slyke, have to be used to avoid this. In determining the CO₂ combining power the blood is previously exposed to alveolar air or a mixture containing 5 to 6 per cent. carbon dioxide. This gives the alkali reserve of the blood (see p. 225).

Another form (Van Slyke's) commonly used for determining the CO₂ in plasma is shown in fig. 103. The apparatus is washed out with ammonia to remove the CO₂. A sample (1 c.c.) of blood (or plasma) is placed in A and is drawn into B. By lowering the mercury reservoir (M), 1 c.c. water to wash and subsequently 0.5 c.c. 5 per cent. H₂SO₄ are similarly drawn in and tap T₁ closed. By lowering M further a vacuum is created in B and the CO₂ bubbles off. Subsequently the blood is trapped in D by opening and closing T₂. On raising the mercury and leaving the liquid trapped it passes up E, the CO₂ which has been given off is measured by reading the amount in the burette after bringing the level of the mercury in M to that in the burette to ensure the gas being at atmospheric pressure. It will be understood that for convenience in the illustration M is much too high.

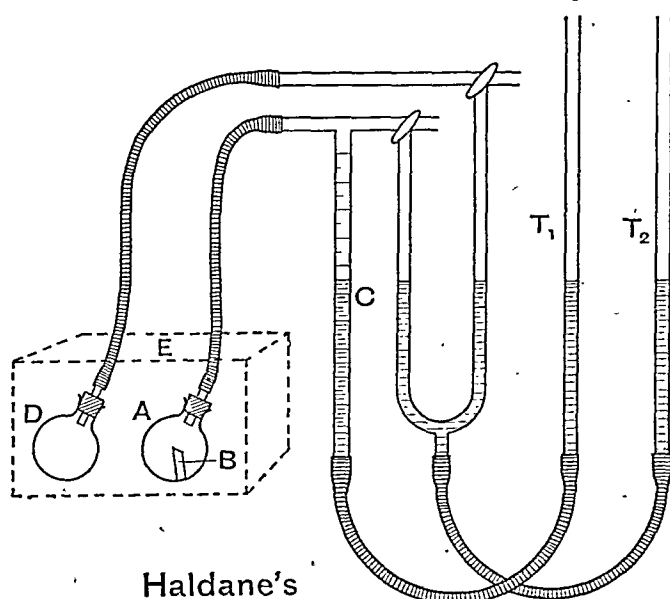
* 0.25 c.c. of 20 per cent. solution.



Barcroft's



van Slyke's



Haldane's

FIG. 103.—Different types of blood gas apparatus.

The oxygen capacity of the blood can also be determined indirectly by estimating the amount of hæmoglobin in the blood and calculating the amount which it will take up. Normal blood contains from 13·5 to 14·5 mg. of hæmoglobin. (See Hæmoglobin.)

The Tension of Gases in Fluids.

In the cases which have been discussed up to this point a condition of equilibrium exists between the gas dissolved in the fluid and the gas in the atmosphere to which the fluid is exposed, so that as many molecules of the gas leave the surface of the fluid as enter it. The gas dissolved in the fluid therefore exercises a pressure which is the same as that of the gas in the atmosphere when equilibrium exists. The word *Tension* is applied to the pressure of the gas in the fluid.

Definition of Tension.—The tension of a gas dissolved in a fluid is equal to the pressure of the same gas in an atmosphere with which the gas in the fluid would be in equilibrium. Above, we have called the pressure which the gas exerts on the liquid P' . If we call the tension of the gas in the liquid T , we find that, when equilibrium exists, $P' = T$. In the case of all true solutions, therefore, we may replace P' in our previous equation by T ; so that: $Q = K \times \frac{T}{P}$. We

thus arrive at a relation between two separate things, which must be most carefully distinguished from one another—the quantity of the gas dissolved in the liquid and its tension.

Measurement of Tension.—Numerous instruments, called *tonometers*, exist for measuring the tension of gases in fluids. Of these, the instrument which has given the most trustworthy measurements of the oxygen and carbonic acid tensions in circulating blood is that invented by Krogh (fig. 104).

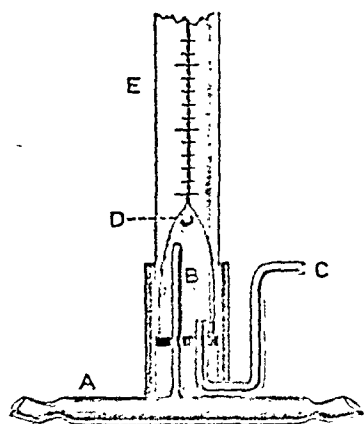


FIG. 104.—Krogh's tonometer.

A T-shaped cannula (A) is introduced into a blood-vessel, say the carotid artery; the blood fills the cavity B and leaves it at C, so that a constant stream of blood is kept flowing. Into it a small bubble of air (D) is introduced. Exchange of gases takes place between the bubble and the blood, and the former very soon gets into equilibrium with the latter. When it has done so,

the bubble is withdrawn up the capillary tube E, taken away, and analysed in a microtonometer gas analysis apparatus.

As an example, suppose the bubble on analysis proved to consist of 4 per cent. carbonic acid and 12 per cent. oxygen, together with nitrogen and aqueous vapour. The gas of the bubble in the instrument was compressed by the pressure of the arterial blood (say 120 mm. of mercury) in addition to the atmospheric pressure of 760 mm. of mercury, and therefore the total pressure was $120 + 760 = 880$ mm. of mercury. Four per cent. of this would have been due to the carbonic acid; 4 per cent. of 880 is 35.2. Twelve per cent. would have been due to the oxygen; 12 per cent. of 880 is 105.6. That is, the carbonic acid and oxygen tensions would have been in round figures 35 and 106 mm. of mercury respectively.

In man it is evident that other methods are necessary.

Barcroft and Nagashiki's method.—If the point of a hypodermic needle fitted to an air-tight syringe is introduced into the radial artery in man a sample of arterial blood may be withdrawn, which may be regarded as of the same composition as that which leaves the lung by the pulmonary vein. If now a bubble of air is introduced into the syringe, this bubble rapidly loses oxygen and gains carbonic acid till it is in equilibrium with the blood, that is to say, till the gases in the bubble exert the same partial pressure as those in the plasma. If the bubble is very small, relatively to the amount of blood, the blood may be regarded as not having changed appreciably in the process, and therefore the partial pressure of the gases found by analysis of the bubble may be taken to be those of the gases in the arterial blood.

Inference method.—This is probably the method most commonly used. A sample of blood is taken and the quantity of oxygen and carbon dioxide in it determined. From a knowledge of the dissociation curves of the blood, which indicate the power of blood to take up gases at different pressures, it can be inferred at what tension the gases must have been present. In accurate investigation it is necessary to make a dissociation curve for the actual blood under investigation, as all bloods are not alike.

The measurement of the gaseous pressures in the mixed venous blood which leaves the right ventricle has been carried out by various methods during the last decade, but the most satisfactory is that of Douglas; a mixture of nitrogen, oxygen, and carbonic acid in suitable proportions is introduced into a large air-tight bag (the Douglas bag is more fully described in fig. 101); the subject takes a deep breath of this and holds his breath for about five seconds. A sample of his alveolar air is then collected, care being taken to leave enough air in the lungs for a second sample to be collected ten seconds later, no breath being inspired in the interval. If the two samples are identical in composition as regards both oxygen and CO_2 , the samples may be adjudged to have been in equilibrium

with the mixed venous blood, and thus the tension of the gases in this blood is ascertained.

Relation between Quantity and Tension of Gases in Blood.

It is now necessary to consider the relationship between these two sets of data.

On page 216 we have seen that for gases in solution in water, $Q = K \times \frac{T}{P}$ where Q is the quantity of gas dissolved, T the tension, K the coefficient of solubility, and P the atmospheric pressure. Since K and P are constant, it follows that Q varies directly in proportion to T ; that is to say, if the tension is doubled, the

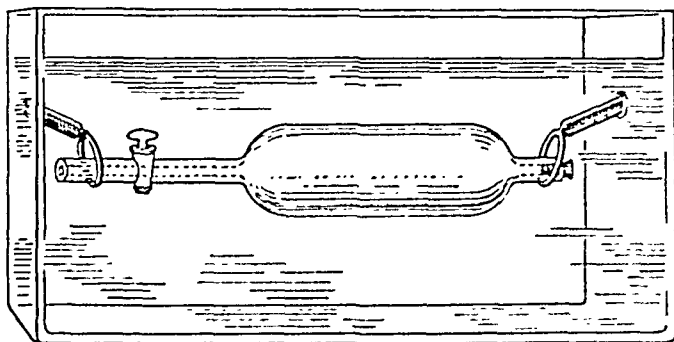


FIG. 105.—Barcroft's saturator, suspended horizontally in warm bath in which it is rotated.

quantity of gas dissolved is also doubled; if the tension is trebled, the quantity of gas is trebled, and so on. These results may be plotted out on a curve in which the quantities are placed on the ordinate and the tensions on the abscissa. Such a curve gives the quantity of gas dissolved at any given tension, and in the case of water the "curve" is a straight line.

But for oxygen and carbonic acid in blood, the curves are not straight lines.

The Transport of Oxygen.—Our knowledge of this subject we owe particularly to the investigations of Barcroft of Cambridge. He has shown how to obtain information regarding the transport of oxygen by studying the amount of oxygen which the blood will hold in varying circumstances. The methods of estimation are described on page 213.

If 100 c.c. of average arterial blood are subjected to a vacuum pump or to the action of potassium ferrieyanide, almost 18.5 c.c. of oxygen are given off, and from what has been said regarding the solubility of gases in water, it is evident this oxygen cannot be in simple solution. The amount in actual solution is only 0.7 c.c.

This capability of the blood to take up large quantities of oxygen depends on the presence in the blood corpuscles of a pigment—hæmoglobin. Blood contains 14 per cent. of this pigment by weight, and each gramme can take up about 1.34 c.c. of oxygen. The actual figure varies in different animals. The chemical characteristics of hæmoglobin are described later.

If, however, the blood is exposed to various tensions of oxygen, it is found that within certain limits the blood takes up oxygen according to the pressure of that gas in the air to which it is exposed. This is seen in the following experiment.

Six vessels, similar to that in fig. 105 (Barcroft's saturator), are taken, and in each is placed a few c.c. of a solution of hæmoglobin, together with gas mixtures of certain definite compositions. Each saturator is rotated in a bath at a given temperature for about a quarter of an hour, by which time the hæmoglobin and the oxygen are in equilibrium. The blood is then withdrawn and the amount of oxygen taken up from the different mixtures determined. The results are expressed as percentages of the maximum which might have been taken up by the blood if it had been exposed to the outside air.

In each instance the mixture is made up to atmospheric pressure by the addition of nitrogen.

Partial Pressure of Oxygen.	Percentage Saturation.
102	97
50	87
20	72
10	55
5	37
0	0

The hæmoglobin which has taken up oxygen we call *oxyhæmoglobin* the remainder without oxygen is called *reduced hæmoglobin*.

These figures may be expressed graphically, and we get the curve which we know as the **dissociation** or **association curve** of hæmoglobin. As we shall see, the partial pressure of 100 is specially important since this is about the pressure in the alveoli of the lungs where the blood normally takes up oxygen. It is seen that at this pressure the blood is 97 per cent. saturated, and for average blood this is equivalent to 18.5 c.c. of oxygen being taken up by 100 c.c. of blood. More recent and more accurate methods indicate, however, that this figure should be 19.5 and some bloods may contain 20 c.c.

The important practical point to notice is the fact that the blood exposed to oxygen at a partial pressure of 100 is almost saturated. The administration of oxygen, therefore, to a normal person cannot

cause the blood to take up much more oxygen than it does from the air normally in the alveoli.

It will be seen that even at low partial pressures the hæmoglobin takes up considerable quantities, but it is evident that while this might be advantageous from the point of view of loading,

Total Hæmoglobin 100

Percentage of reduced hæmoglobin Percentage of Oxyhæmoglobin

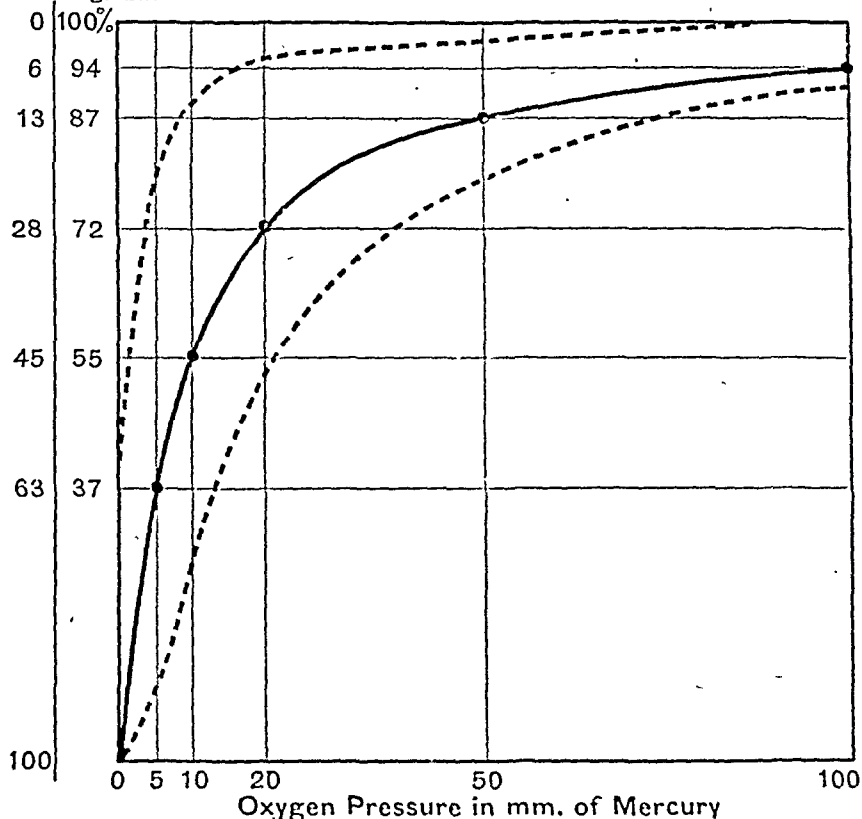


FIG. 106.—Dissociation curves of hemoglobin solution in water at 37° C. Blue, reduced hæmoglobin; red, oxyhæmoglobin. The dotted line in the blue is the curve obtained when the blood is cooled to 16° C. The dotted line in the red indicates the effect of heat and salts. Increasing the amount of CO_2 in the gas mixtures similarly moves the curve to the right. (After Barcroft.)

it would be unsatisfactory from the point of view of giving up oxygen.

But blood is not a solution of hæmoglobin. In blood the hæmoglobin is contained in corpuscles, and in these is present in close association with its many salts. By adding such salts to hæmoglobin in a saturator, it may be shown that they prevent the hæmoglobin from holding so much oxygen at the lower concentrations. Carbon dioxide has a similar effect which is shown by the dotted lines in fig. 107.

The effect of carbon dioxide is interesting, as the amount used in the experiment is that which is normally present in the air of the alveoli. The reason for this effect of the carbon dioxide on the amount of oxygen held, we shall see, is that the oxygen and the carbon dioxide indirectly compete for the available alkali in the corpuscles of the blood.

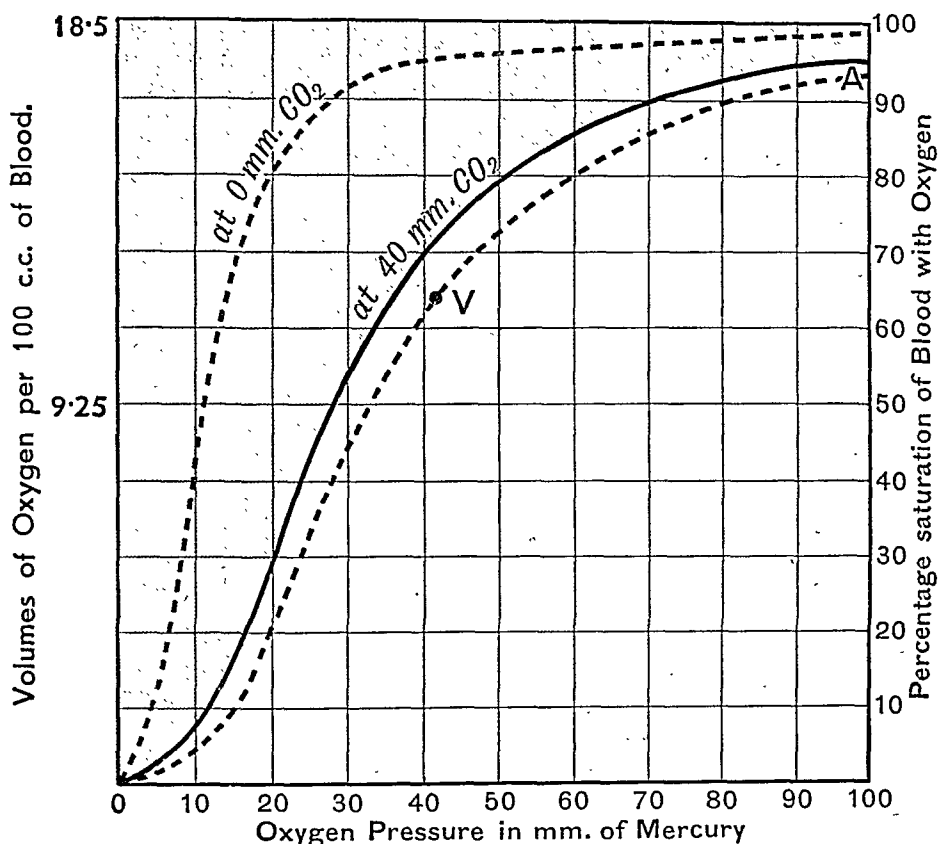


FIG. 107.—Dissociation curve of haemoglobin in the actual blood at 37° C. and 40 mm. CO_2 . Blue, reduced haemoglobin; red, oxyhaemoglobin. The dotted curve in the blue is the dissociation curve at the same temperature, but at 0 mm. CO_2 . Note the resemblance of this to the haemoglobin curve. The addition of small amounts of acid or more CO_2 would move the whole curve to the right. A indicates the average content and tension of arterial blood; V, those of venous blood. (After Barcroft.) The atmospheric pressure at the summit of Mt. Everest (29,000 ft.) is about 250 mm.

The two coloured figures (106 and 107) should be carefully compared, as they show graphically the advantages of blood over a pure solution of haemoglobin as an oxygen carrier.

These factors, however, not only affect the amount of oxygen which the blood gives off, but also the rate at which the oxygen is liberated. At room temperature, oxygen is taken up rapidly and given up slowly, but at body temperature the rate of giving up is enormously increased.

The Transport of Carbon Dioxide.—The carriage of carbon dioxide has been studied by the same methods as those used for oxygen. The estimation of carbon dioxide has already been described. Since in solution it is an acid of some power, special arrangements have to be made for its transport from the active tissues to the lungs to prevent its causing any marked change in the hydrogen-ion concentration of the blood. This is accomplished by the carbon dioxide entering into chemical combination in the tissues and being set free again when it reaches the lungs, but in this process both the corpuscles and the plasma play a part.

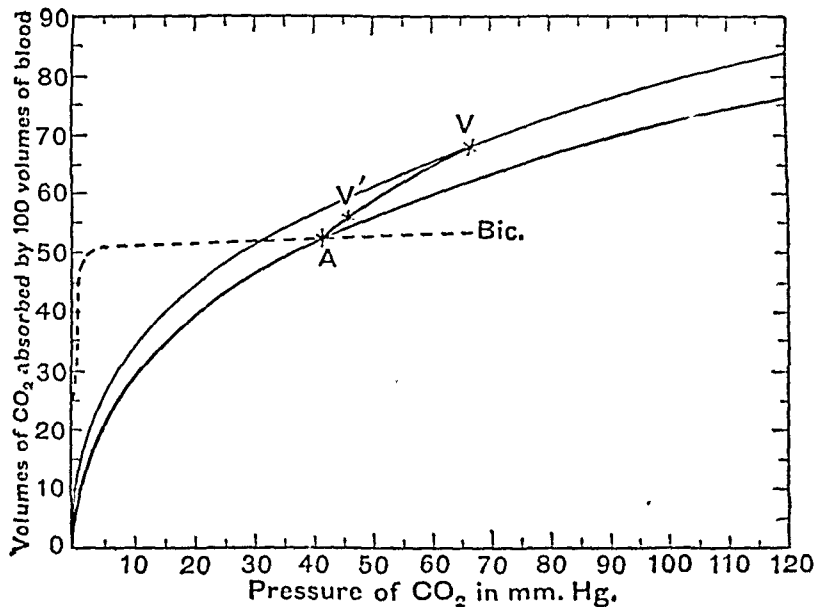


FIG. 103.—Dissociation curve for carbon dioxide in blood. The points A and V are the same as those in fig. 107 (Wright, after Haldane). The dotted line is the dissociation curve of a solution of sodium bicarbonate.

It is convenient to visualise the carbon dioxide as being loaded into the blood by the exposure of the blood in the tissues to an atmosphere containing a high concentration of carbon dioxide, just as carbon dioxide is forced into aerated water from cylinders under pressure in a factory, the reception of the carbon dioxide being, as in the case of soda-water, facilitated by alkali which prevents the water becoming unduly acid. The pressures concerned in the body, however, are not so great.

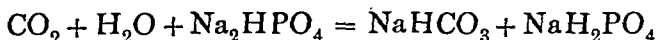
It must, however, be understood that the taking up of carbon dioxide in the tissues and its giving off in the lungs by the blood are essentially dependent on differences in partial pressures and that it is easily possible to construct a carbon dioxide dissociation curve in the same way as has been done for oxygen (fig. 108).

The venous blood contains about 58 c.c. per cent. of carbon dioxide during rest but appreciably more during activity while the arterial blood contains 54 c.c. per cent. of carbon dioxide (*i.e.* more than twice amount of oxygen).

These figures emphasise that during rest a very small proportion of the carbon dioxide in the venous blood is mobile and lost in the lungs and that the arterial blood contains more than twice the amount of carbon dioxide than oxygen. This level of carbon dioxide is kept constant by the respiratory apparatus.

The Arterial or Constant Carbon Dioxide.—By this is meant the carbon dioxide which is present in the arterial blood which does not come off in the lungs, but which can be driven off by the addition of a stronger acid such as tartaric. This is present for the most part in the form of sodium bicarbonate and constitutes 90 per cent. of that present in the blood during rest.

The alkaline reaction of the bicarbonate is balanced by the presence in the plasma of carbon dioxide in simple solution to the extent of $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3} = \frac{1}{20}$. The hydrogen-ion concentration of blood that is in contact with the tissues normally depends on this ratio. The presence of the phosphate buffers in the plasma ensures an adequate supply of bicarbonate according to the reaction,



while any tendency for the dissolved carbon dioxide and the hydrogen-ion concentration of the plasma to rise is at once corrected by an increased respiratory activity. The acid phosphate is excreted by the kidney. Even the arterial carbon dioxide can, however, be reduced by over-ventilation of the lungs or increased by inadequate ventilation.

The Mobile Carbon Dioxide, although in no way different from the more constant fraction, is characterised by being taken up and given up by the blood at a great speed which has been shown by Roughton and his co-workers to depend on the presence of an enzyme, *carbonic anhydrase*, which catalyses the reaction $\text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3$. This enzyme is present only in the corpuscles, from which it can be extracted with 40 per cent. alcohol. Its activity is inhibited by cyanides.

In the transport of this mobile fraction the reduction of hæmoglobin in the tissues plays an important part, for the oxy-hæmoglobin which is reduced in the tissue is more strongly acid than reduced hæmoglobin.

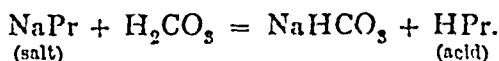
The high concentration of the carbon dioxide makes it diffuse into the corpuscle rapidly and under the influence of the carbonic

anhydrase it rapidly becomes H_2CO_3 , which at once dissociates and takes the place of the oxygen which has left the corpuscle. The products of the dissociation HCO_3^- and H^+ probably attach themselves for the most part to the potassium hæmoglobinate and the hæmoglobin to form KHCO_3 and HHb . A proportion of the CO_2 may combine direct with the NH_2 group of the hæmoglobin to form a carbamino compound, HbNHCOOH .

The balance between the positive and negative ions in the corpuscles and the plasma is upset, but this is at once corrected and equilibrium on both sides of the corpuscular membrane re-established by the passage of Cl^- ions* into corpuscles when the HCO_3^- diffuses out.

This reaction which is known as the *chloride shift* was first brought to notice by the fact that there is a reduction of the chloride content of the plasma when carbon dioxide is added to blood while there is at the same time an increase in the amount of sodium bicarbonate in venous blood which is balanced by CO_2 in solution. This permits the hæmoglobin to assist in the carriage of CO_2 without any change in blood reaction (Hamburger).

The proteins of the plasma play a small part in the carriage of carbon dioxide since they are able, like feeble acids, to combine with bases which, however, can be removed from them by an acid stronger than themselves. We have therefore such reactions as—



Because of such reactions the dissociation curve of a bicarbonate solution is not exactly the same as that of separated plasma (fig. 108).

All these very complicated reactions are rendered necessary by peculiar properties of the membrane of the red blood-corpuscle through which the cations K^+ and Na^+ cannot pass easily, although the anions HCO_3^- and Cl^- can do so.

It will be seen that when carbon dioxide is added to the blood the corpuscle does not change its reaction because the place of the oxyhæmoglobin is taken by H^- and Cl^- ions.

Similarly in the plasma there is no change of reaction because HCO_3^- takes the place of Cl^- ions.

In the lungs the whole process is the reverse of that in the tissues, the loss of carbon dioxide being brought about by its low tension in the alveoli and the formation of the acid oxyhæmoglobin.

These changes have all been conveniently summarised by Roughton, a modification of whose figure is given on p. 225.

* These Cl^- ions are in association with Na^+ ions in the plasma which now become associated with HCO_3^- ions.

Alkali Reserve (Van Slyke).—The alkali available for the transport of acid is known as the *alkali reserve of the blood* and may be estimated directly, by finding the **carbon dioxide combining power** of the blood. This is determined by exposing a sample of blood to alveolar air or a gas mixture with the same

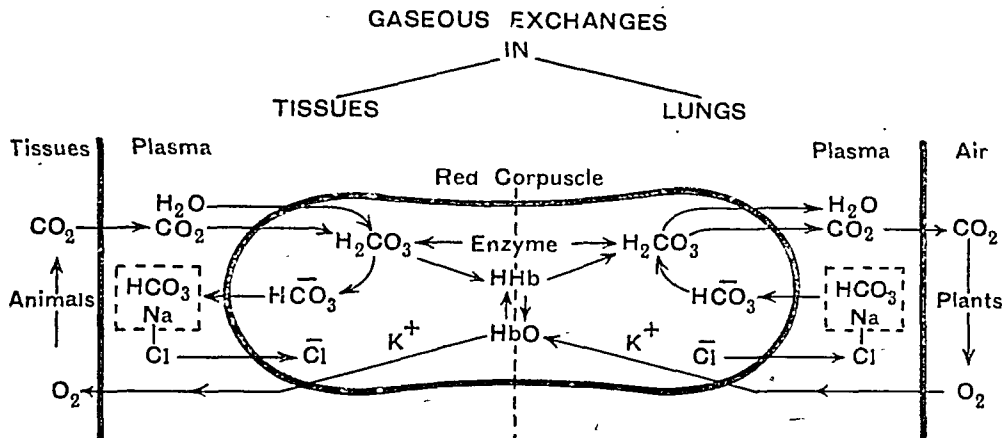


FIG. 109.—The oxygen cycle and the carriage of carbon dioxide by the blood (see p. 224).

amount of carbon dioxide (5.5 per cent.) and subsequently finding the amount of carbon dioxide which has been taken up. This latter determination may be made by the Van Slyke, Haldane, or Barcroft apparatus (fig. 103, p. 215). Clearly, if any acid is being added to the blood, alkali is taken up and the alkali reserve becomes appreciably reduced. If, for any reason, such as the excessive loss of carbon dioxide at high altitudes, there is less acid in the blood than normal, the alkali reserve becomes reduced by the excretion of base by the kidney to keep the reaction of the blood at its normal level.

The body has many other ways for maintaining its neutrality in many varying circumstances, but we cannot profitably deal with these until we have considered the various other mechanisms concerned, especially those of the kidney. The alkali reserve of the body is dealt with later.

In conditions of severe muscular work not only carbonic acid (carbon dioxide and water) is produced but also lactic acid which combines with the alkali of the blood to form lactate, some of which is excreted by the kidney (see also "Oxygen Debt").

It is important also to remark that CO_2 is got rid of by the kidney as well as by the lungs, and in cases of long obstruction to the respiratory tract this other means may become very important.

The Mechanism of Gaseous Exchange in the Lung.

1. *Oxygen*.—The simplest explanation of the passage of oxygen from the alveolar air into the blood is that the process is a purely physical one of diffusion. (See Diffusion.)

The conception of respiration based on this view would be that the pressure of oxygen in the air of the alveoli, though less than that in the atmosphere, is greater than that in venous blood; hence oxygen passes from the alveolar air into the blood-plasma; the oxygen immediately combines with the hæmoglobin, and thus leaves the plasma free to absorb more oxygen; and this goes on until the hæmoglobin is entirely, or almost entirely, saturated with oxygen. The reverse change occurs in the tissues where the partial pressure of oxygen is lower than in the plasma, or in the lymph that bathes the tissue elements; the plasma gives up its oxygen to the lymph, the lymph to the tissues; the oxyhæmoglobin then undergoes dissociation to supply more oxygen to the plasma and lymph, and thus in turn to the tissues.

Some authorities have considered that in cases of definite oxygen-want, such as during violent muscular exercise, or on the tops of high mountains, the lining epithelium of the pulmonary alveoli can, by a process of active secretion, like that of the swim bladder of a fish, transfer oxygen from the alveolar air to the blood. Barcroft lived for six days in a respiration-chamber in which the oxygen pressure in the inspired air was gradually reduced from 130 mm. Hg on the first day to 84 mm. on the last; a pressure of 84 mm. Hg corresponds to that experienced at an altitude of about 18,000 feet. At the close of the experiment a cannula was inserted into Barcroft's radial artery so that his arterial blood could be collected either when he was at rest or performing work; his alveolar air was collected and examined simultaneously. The percentage saturation with oxygen was measured in the blood samples and its tension inferred from the dissociation curve. The following results were obtained:—

	During rest.	During work.
Pressure of oxygen in alveolar air . . .	68 mm. Hg.	57 mm. Hg.
Tension of oxygen in arterial blood . . .	60 ,,	48 ,,

In researches Krogh's bubble aerotonometer has been applied to man, the blood being withdrawn from an artery by a hypodermic syringe. By this method comparisons have been made of the oxygen-tension in the arterial blood and alveolar air, both at the sea-level and at Cerro, a mining town in the Andes (14,200 ft.). In both cases equilibrium seems to be attained so closely that the difference between the two is within the region of experimental error:—

	Barometric pressure.	O ₂ pressure in alveolar air.	O ₂ tension in arterial blood.
Cambridge	761 mm. Hg.	100 mm.	99
Cerro	458 ,,	58 ,,	56
Edinburgh	755 ,,	102 ,,	101
Mt. Everest	250 ,,	not available	

Many experiments have also been carried out on animals, especially by Krogh who varied the oxygen content of the alveolar air. In no instance, however, has it been found that the tension of the oxygen in the arterial blood is ever above that in the alveoli.

2. *Carbonic Acid*.—The dissociation of carbon dioxide from the blood takes place in the lung by the reverse processes from those which have just been described for its transport. The chief factor is the fall of the tension of carbon dioxide in the lungs (42 mm.)

THE GASEOUS TENSIONS IN THE HAEMO-RESPIRATORY SYSTEM in mm. Hg.

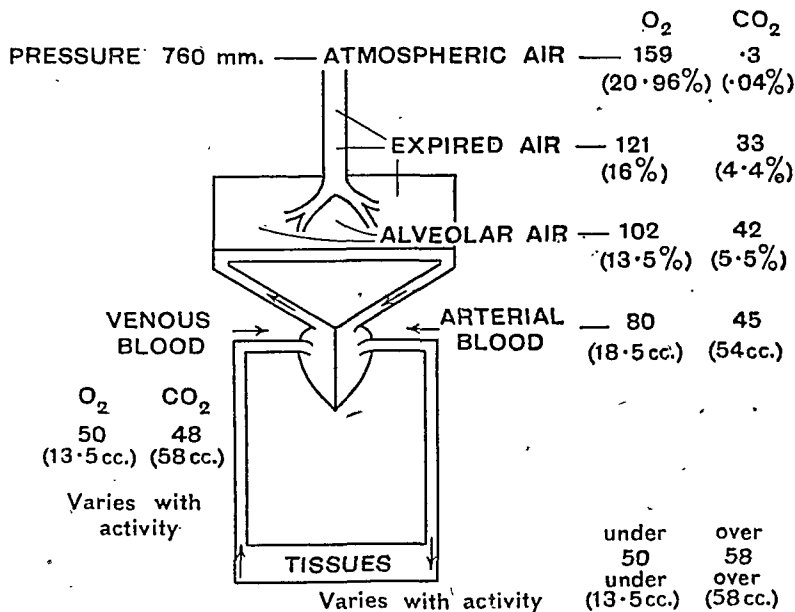


FIG. 110.

compared with that at which it has been loaded (over 58). The process is facilitated by the formation of oxyhæmoglobin, which tends to drive the HCl from the corpuscle into the plasma; the HCl breaks up the NaHCO_3 and drives off the CO_2 into the alveolar air.

In addition the dissociation of the carbon dioxide attached to the hæmoglobin is greatly speeded up by the presence of the enzyme carbonic anhydrase in the corpuscles.

The tension of the carbon dioxide in the tissues is usually over 58, but there is considerable variation in the different body fluids according to their reaction.

The above figure summarises the main facts in relation to the two gases. These figures are approximate and may be taken as averages for the body at rest. It is seen that the equilibration is almost com-

plete in the lungs but not quite. In exercise the figures for CO_2 in the tissues may be much increased and those for the O_2 correspondingly reduced. Actually also, for reasons to be described in relation to the respiratory quotient, the blood gives up in the lungs slightly less carbon dioxide than the amount of oxygen it receives. Some of the oxygen is used to oxidise hydrogen and is excreted as water (H_2O).

CAUSE AND REGULATION OF PULMONARY VENTILATION.

The Function of the Control of Respiration.—The control of respiration is of the greatest importance in relating the extent of the pulmonary ventilation to the needs of the animal. It provides a means by which both the depth and rate of the respiratory movements may be increased, while at rest there is a minimum pulmonary effort.

There are three factors, each of which plays a part in maintaining and regulating the rhythmic movements of respiration. They are the respiratory centres, the vagus nerves, and the chemical condition of the blood.

(1) **The Respiratory Centres.**—If sections of the brain stem are made from above downwards all forms of respirations cease when the tip of the calamus scriptorius* is reached. For this reason Legallois (1811) who first did the experiment, called this region the respiratory centre. The work of Lumsden, however, shows that respiration is affected by section of the brain at a much higher level. Section obliquely through the upper part of the pons results in the production of apneustic respiration, *i.e.* respiration which has a prolonged inspiratory phase, while after section through the middle of the pons gasping is the only type of respiration seen (fig. 111). These stages are readily seen if an animal is bled to death, when we may assume that the different parts of the respiratory mechanism fail from above downwards. In man these phenomena are also seen at the approach of death.

The respiratory centre has been now shown to consist of two parts, an inspiratory centre in the formatio reticularis over the inferior olive and an expiratory centre which is just above and dorsal. Each may be stimulated separately to produce inspiration and expiration. Of these two the inspiratory centre is much the more active as expiration is assisted by the recoil of tissues. The respiratory centres are normally affected by chemical and nervous stimuli.

(2) **The Chemical Control of Respiration.**—The importance of the chemical stimuli was fully demonstrated and studied by Haldane and his co-workers, especially Douglas and Priestley in Oxford.

* This is the name given to the lower part of the floor of the 4th ventricle in the medulla which is shaped like a pen.

The Role of Carbon Dioxide.—In the first place, they introduced the simple method of obtaining a sample of the air in the alveoli (see fig. 100, p. 207). They found that, under constant atmospheric pressure, the carbon dioxide exerts an almost constant pressure in the alveolar air of the same person. In different individuals this pressure varies somewhat but averages about 40 mm. Hg (5 to 6 per

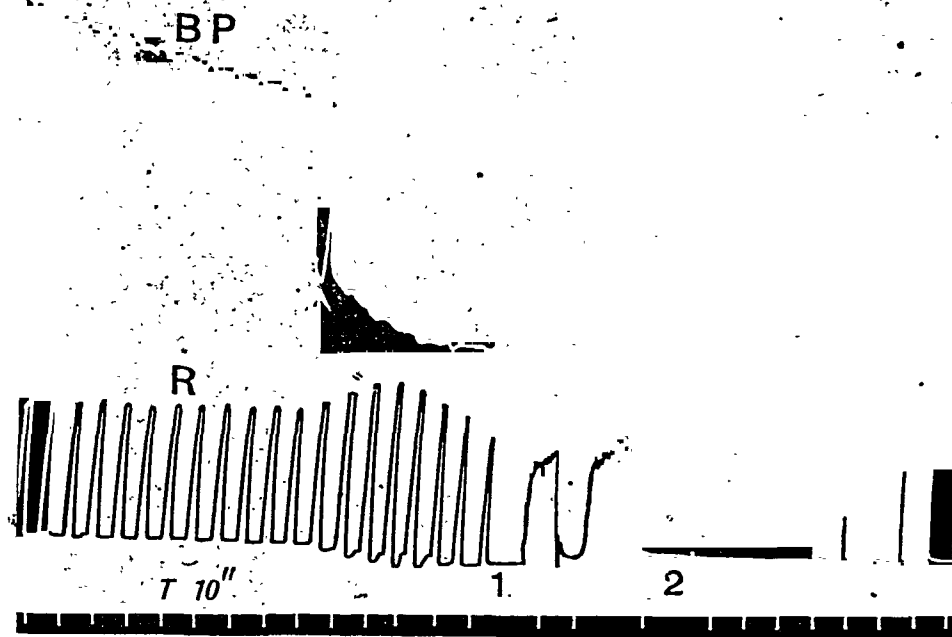


FIG. 111.—A composite tracing showing different types of respiration produced by very severe hæmorrhage at the point where the abrupt fall in blood-pressure is seen. Pieces of tracing were removed at 1 and 2 for convenience of reproduction. First, normal respiration is seen which becomes deeper and subsequently shallower; between 1 and 2 are seen two respirations of the apneustic type, which may be absent if the hæmorrhage is rapid; after is seen the typical gasping. In some instances different types of respiration may gradually become superimposed on each other, e.g. the gasping may gradually come on during failing normal or apneustic respiration. The blood-pressure recorder was removed later to prevent damage of the respiratory record. (McDowall.)

cent. of an atmosphere) the pressure of the atmosphere in the alveoli at sea-level being 760 mm. less 17 mm. for water vapour.

They found that a rise of 0.2 per cent. in the alveolar **carbon dioxide** is sufficient to double the pulmonary ventilation during rest. This effect of carbon dioxide can readily be shown by causing an individual to breathe a mixture of 95 per cent. oxygen and 5 per cent. carbon dioxide. If, on the other hand, an individual breathes more deeply and rapidly than he does normally at rest, i.e. until the air in the alveoli becomes more like that of the atmosphere and the carbon dioxide percentage in the lungs falls, respiration ceases for a short time. This cessation is known as **Apnoea**. It was once thought to be due to over-oxygenation of the blood, but it is now

known that this cannot occur, since the arterial blood is almost fully oxygenated with normal respiration. That the distension of the lungs is not responsible is shown by the fact that, if the over-ventilation is carried out with expired air, no such apnœa occurs.

It should be noted, however, that in a number of persons apnœa is not produced by over-breathing. Whether or not apnœa occurs would appear to depend on the state of the nervous system. In some persons the effort of the over-breathing on the chemical substances it produces more than counter-balances the loss of carbon dioxide. Nor does the occurrence of apnœa run parallel to the production of a fall of arterial pressure (see p. 158). The latter was absent in J. S. Haldane although the apnœa was well marked, while the reverse was true of Boothby. (Boothby.)

From what we have said in relation to the exchange of gases in the lungs it is evident that the changes in the gaseous content bring about similar changes in the arterial blood. It is these changes in the gaseous content of the blood which really cause the alteration in the respiratory movements. The final proof of this was given by Fredericq (1885) of Liège in crossed circulation experiments, in which the respiratory centre of one animal was kept alive with blood from another; it was shown that the inhalation of carbon dioxide by the donor caused an increased respiration in the animal supplied and over-ventilation of the donor the reverse. The cessation of respiration is the result of a fall of arterial carbon dioxide consequent on the reduction of the amount of that gas in the alveoli. In man this may fall to less than half the normal 5-6 per cent., but breathing is resumed before the normal is reached again, since the cessation of breathing eventually causes oxygen-want which stimulates respiration reflexly *via* the carotid and aorta (see below).

The Role of Oxygen Want.—That oxygen-want alone may cause increase of respiration is shown by causing an individual to re-breathe his own expired air, at the same time preventing an accumulation of carbon dioxide by passing the air through soda lime. The increase, however, is slight compared with the effect of carbon dioxide. But for this fact respiration would cease at high altitudes where, for example, the partial pressure of alveolar carbon dioxide may be 28 mm. Hg instead of the normal 40 at sea-level.

In similar experiments it has been found that asphyxia of an animal, excluding its brain, causes increased respiration. There is now ample evidence that carbon dioxide acts not only on the medulla but on the spinal cord, the *carotid bodies** and the

* The carotid bodies are a minute structure close to the carotid sinus at the bifurcation of the carotid arteries largely composed of minute vessels and supplied with nerves from the glossopharyngeal like the sinus. The aortic body is a similar structure in relation to the aorta.

aortic body. The action on the aorta is seen in the fact that the effect of carbon dioxide is reduced by section of the aortic nerves. These regions are also sensitive to oxygen-want (Heymans). The stimulation of the carotid bodies can be shown by perfusing them with blood of differing gaseous composition. The respiratory centres on the other hand rapidly fail if subjected to oxygen-want, *e.g.* by hæmorrhage (fig. 111) or by compression of the carotid and vertebral arteries which supply the brain.

We now see how the increased respiration caused by exercise is brought about. If the pulmonary ventilation is not sufficient to maintain the arterial carbon dioxide and oxygen at their normal levels (as in exercise when the blood reaching the lungs is excessively venous), the respiratory centre is stimulated by the blood and respiration is increased. In severe exercise the respiratory centre is still further excited by the lactic acid which is produced by the active muscles in addition to carbon dioxide.

Thus we see that respiration depends on metabolism, or more accurately on the carbon dioxide produced and the oxygen used by the tissues, and as we shall see later, the tissues which can affect the total metabolism most are the voluntary muscles.

Forced breathing, since it causes the body to lose carbon dioxide, has a profound effect on the acid-base equilibrium of the body (see later Chapter).

The Specific Respiratory Stimulus.—If any acid is injected into the circulation an increase in respiration occurs and it has been debated whether or not it is the increased hydrogen-ion concentration rather than the carbon dioxide *per se* which is the real stimulus. That the former is not the case, however, is suggested by the fact that although the blood of an animal is made alkaline (and this degree is never reached during apnoea) by the injection of alkali, breathing still continues although slightly depressed.

Further, it has been found by Hooker that a given rise of hydrogen-ion concentration produced by CO_2 is much more effective as a respiratory stimulus than the same concentration produced by another acid.

The explanation for this has been afforded by Jacobs. By studying the reactions within cells he established that the power of H_2CO_3 , *i.e.* $\text{H}_2\text{O} + \text{CO}_2$, to penetrate through cell membranes is very much greater than that of any other acid. It is therefore, presumably, the best stimulant of the cells of the respiratory centre.

We may look upon carbon dioxide as a specific stimulus only in the sense that it permeates more rapidly and we may consider that other acids, *e.g.* lactic, will stimulate the centre, not only by increasing the hydrogen-ion concentration of the blood, but also by producing carbon dioxide from the bicarbonate of blood.

(3) **The Nervous Control of Respiration.**—Respiration is influenced by sensory nerves generally, by the vagi, and by the higher centres.

Sensory Nerves.—Stimulation of any sensory nerve causes increased respiratory movements if the anæsthesia is not too deep. In operations especially on the chest, this may lead to the inhalation of an overdose of an anæsthetic and also to the washing out of carbon dioxide. The consequent cessation of respiration may be fatal. Artificial respiration together with sensory stimulation by rubbing the chest and pulling on the tongue is then necessary.

If the vagi are cut or blocked in an animal deeply anæsthetised with chloral or morphine, the respiration becomes markedly slow and

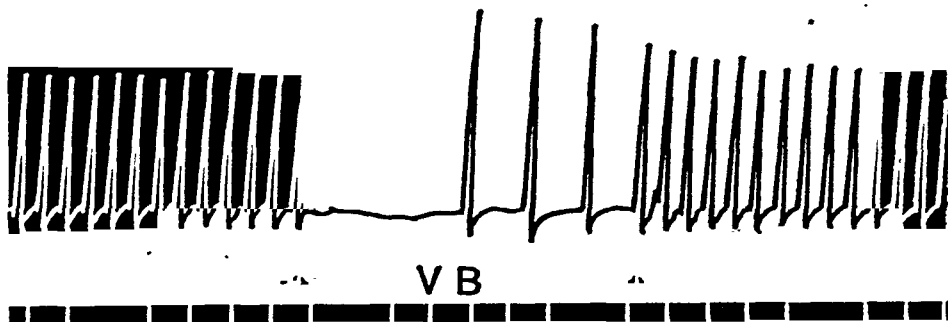


FIG. 112.—A record of respiration from a cat anæsthetised by chloralose and rested. Between the arrows both the vagi were blocked by an electric (galvanic) current. Note the slow deep respirations which result from the loss of the Hering-Breuer reflex (McDowall).

deep. These facts were investigated by Hering and Breuer in 1868, and they described what we now know as the *Hering-Breuer reflex*, in which impulses pass up the vagi and cut short each respiratory phase. Respiration is thereby rendered less deep than it otherwise would be.

We have also evidence that nervous impulses pass up the vagus whenever the lung is artificially inflated or deflated; but whether the impulse during the expiratory period is inhibitory to an expiratory centre, or a stimulus to an inspiratory centre, is difficult to decide. The general evidence available suggests that there are really two centres acting reciprocally.

The subject was reinvestigated by Head, who for this purpose recorded the movements of a slip of diaphragm, which in the rabbit can be separated with its nervous and blood supply intact.

In one series of experiments *positive ventilation* was performed; that is, air was pumped repeatedly into the lungs, and so increased

their normal distension; this was found to decrease the inspiratory contractions of the diaphragm, until at last they ceased altogether, and the diaphragm stood still in the expiratory position (fig. 114, A). Negative ventilation brought the diaphragm to inspiratory standstill.

Later investigations, in which oscillographic records have been taken of the action potentials of the vagus, however, have shown

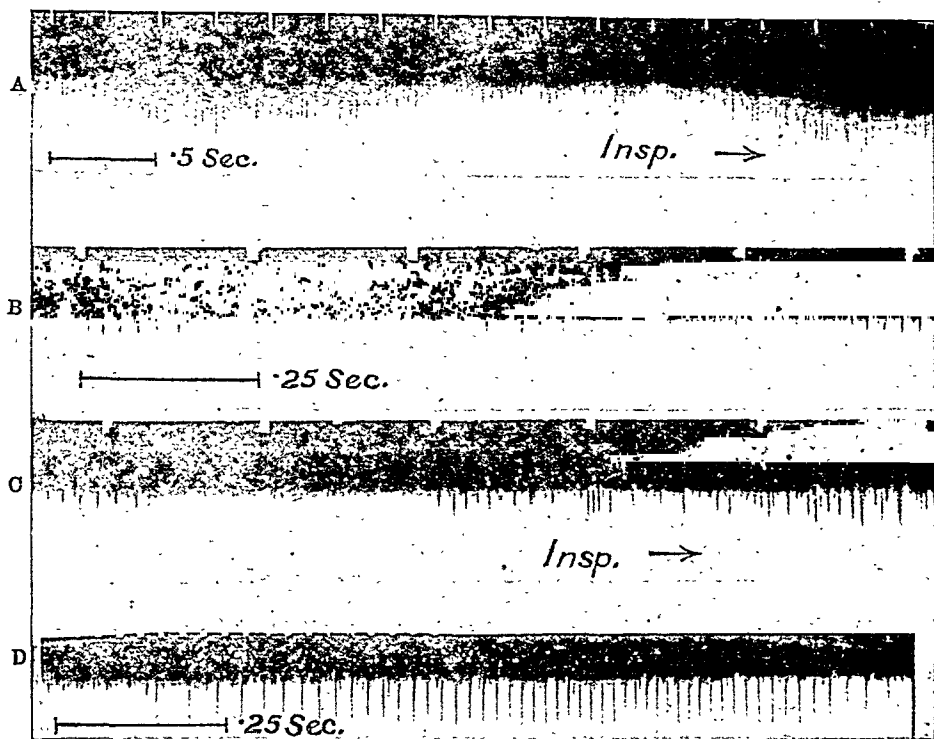


FIG. 113.—Records made with valve amplification and a Matthews' oscillograph to show the afferent impulses passing up the vagus in the cat. All but a few of the nerve-fibres have been divided. In B and C only one cardiac fibre is in action and in D only one fibre from the lungs.

A. Decerebrate cat. Record showing the discharge of impulses at each heart-beat (in nerve-fibres corresponding to those of the cardiac depressor nerve in the rabbit) and at each expansion of the lungs (inspiration).

B and C. From another preparation made at a higher speed to show the individual impulses. B shows three groups of cardiac impulses. In C the onset of the inspiratory discharge is shown as well.

D. The discharge of impulses in a single fibre of the vagus during inspiration. The impulses occur in a regular series with a frequency which rises to a maximum at the height of inspiration. (E. D. Adrian.)

that in normal quiet respiration the impulses which pass up the nerve during inspiration are much more marked than those during expiration; indeed, during the latter phase they may be negligible.

Lumsden has also shown that the passage of air over the mucous membrane of the air-passages may act as an inhibitory stimulus.

If the vagi are cut, these inhibitory impulses are then absent, and respiration must depend on chemical stimuli. Why, however, inspiration and expiration should still alternate is as yet unknown.

Similarly, *stimulation* of the central end of the vagus, by setting up artificial inhibitory impulses, causes an inhibition of respiration in whatever phase respiration is at the time of the stimulation.

It is now evident the vagi also carry accelerator nerves, for it has been found by Hammouda in Anrep's laboratory that if they are cooled their stimulation results in acceleration. The slowing which occurs on section may therefore be considered to be due partly to the cutting off of accelerator impulses which arise at the periphery.

There is, however, evidence that the Hering-Breuer reflex is not constantly in operation, otherwise we should not be able to breathe deeply during exercise. This may be shown experimentally. By using a block with a galvanic current, it has been shown that

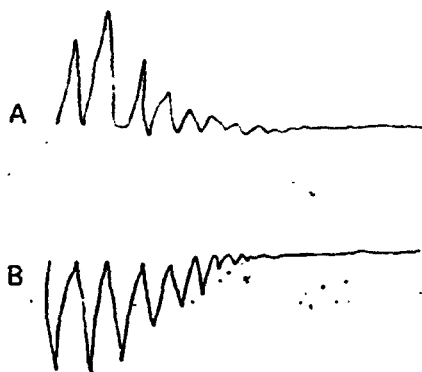


FIG. 114.—Tracings of diaphragm. The upward movements of the tracings represent inspiration; the downward movements, expiration. A, result of positive, B, of negative ventilation. (After Head.)

the effect of the vagi on the respiratory centre may be made to vary. Thus, although at first, while the animal is under ether anaesthesia, block or section of the vagi may have no effect whatever on respiration (McDowall), if the animal is allowed to rest under chloralose anaesthesia, the classical effect is obtained on blocking. Again, it may be shown that asphyxia, sensory stimulation, or the injection of acid and adrenaline reduces or abolishes the effects of vagus section altogether. The Hering-Breuer reflex is, therefore, to be considered a mechanism for the limitation of respiration especially during rest, somewhat analogous to the depressor reflexes of the circulation.

Shallow and Rapid Respiration.—This condition may be produced by irritating the inside of the alveoli with a gas such as chlorine (one of the poison gases used in war). It may also be produced

by sudden blocking of the pulmonary artery or its branches (embolism). Experimentally this has been done by injecting oil intravenously (Dunn); see fig. 115.

The reflex origin of such respiration is shown by the fact that it disappears if the vagi are cut, and its importance lies in the fact that it occurs in pneumonia when it causes faulty aeration of the blood.

The irritation of the vagus-endings in the lung may be considered to stimulate the centres and cause exaggeration of the Hering-Breuer reflex. Such a condition may be due also to a gradual weakening of the respiratory centre, such as occurs during deprivation of oxygen or lessening of the oxygen intake below a certain level; or again tachypnoea, the rapid respiration induced in some animals by heat, may be purely central, and may be produced by merely warming the blood as it goes to the brain.

Exhaustion of the respiratory centre may be brought about by prolonged and forceful breathing through narrow tubing. Hence the necessity for wide-bored tubing in divers' apparatus and the like.

The Essential Nature of Respiration.—Discussion is frequent on the question whether respiration is essentially a reflex phenomenon, the so-called respiratory centres being merely synapses or central cells upon which carbon dioxide and oxygen act. That carbon dioxide is essential for much nervous activity is well known; it is, for example, essential for the normal response of the vasomotor centre to posture and the maintenance of decerebrate rigidity. It has been suggested that afferent impulses from the sensory nerves generally bring about inspiration, while expiration is a reflex response to afferent impulses arising from the inspiratory muscles. The other view is that the centres of the brain are constantly giving off rhythmical stimuli to the respiratory muscles in virtue of their inherent rhythm.

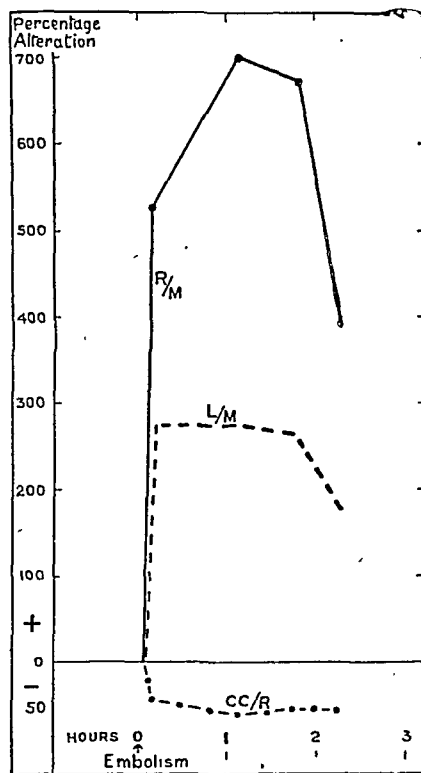


FIG. 115.—Chart showing percentage alteration in rate of respiration (R/M), total ventilation of the lungs (L/M), and depth of each respiration (CC/R) during the course of an experiment in which pulmonary embolism was produced in a goat. The zero line represents the normal for each factor, and variations in each are recorded in percentage terms of the normal, so as to make all comparable. As the percentage rise in rate exceeds the percentage rise in ventilation, the depth of breathing falls below the normal. (J. S. Dunn.)

This view has been strongly supported by Adrian, who has found that if electrodes are placed on the brain removed from a goldfish, groups of action potentials may be recorded which correspond in rate to gill movements. In the fish these are respiratory movements.

This experiment appears to supply the hitherto unobtainable proof that the brain can set up rhythmical impulses for respiration in the absence of receipt of afferent impulses. Hitherto it has not been possible to obtain evidence of respiratory activity without making use of some respiratory movement which in itself may be the origin of afferent impulses. In the mammal it is also impossible to cut off all afferent stimuli without so injuring the blood supply that the brain dies, for the central respiratory mechanism dies rapidly when the blood supply ceases.

In connection with the relative importance of the nervous and chemical factors in breathing, it was at one time held that if the vagi were cut carbon dioxide could not cause an increased rate of respiration. Scott, the author of this view, has now withdrawn it since further experiments have proved it to be untenable. Even when these nerves are divided, an increase in rate can be produced by causing the animal to re-breathe its own expired air provided all other sensory stimulation has been avoided (McDowall).

The Effect of Higher Centres.—Krogh pointed out that at the onset of exercise the increase in total ventilation may be immediate, and may take place before any chemical changes could have occurred in the blood. This may be shown by causing an individual to work a stationary bicycle with an electro-magnetic brake the strength of which can be altered without the knowledge of the subject. With an increase of load, the subject's respiration is at once augmented; but not only so, for a similar augmentation occurs if he sees the switch being moved and thinks the loading current has been thrown in. The initial increase in total ventilation would therefore appear to be effected by the higher regions of the brain.

To sum up:—In a normal respiration the chemical and nervous factors would therefore appear to be related somewhat as follows: The inspiratory centre is stimulated to a degree depending on the gaseous content of the blood, but the movement is cut short by an inhibitory impulse passing up the vagus, only to begin again when the effects of this inhibitory impulse are removed.

The First Inspiration.—During foetal life the need of the embryo for oxygen is small, and is amply met by the transference of oxygen from the maternal blood through the thin walls of the foetal capillaries in the placenta. But when the child is born, this source of oxygen is no longer available, the increasing vascularity of

the blood stimulates the respiratory centre to action, and is the essential cause of the first inspiratory efforts the new-born child makes to obtain the oxygen it requires. It is said that if the placental circulation is stopped while the child is still *in utero*, respiratory efforts are also made. Some regard the action of the air on the body surface as an accessory cause of the first respirations, and it is the practice to increase this in feeble children by stimulating the cutaneous nerves by the application of cold water to the skin. Such treatment always causes deep inspirations, even in the adult.

Inhibition of respiration may be brought about in several ways: for instance, stimulation of the central end of the glossopharyngeal inhibits the respiratory movements for a short period; this accounts for the very necessary cessation of breathing during swallowing. Stimulation of the central end of the cut superior laryngeal nerve or vagus nerve, or of its terminations in the mucous membrane of the larynx, as when a crumb is "swallowed the wrong way," produces an increase of expiratory efforts, which culminate in coughing.

Breaking-Point.—The time which the breath can be held depends on the accumulation of carbon dioxide in the blood. Usually the breaking-point is reached when the carbon dioxide in the alveoli has reached **7 per cent.** - If, however, the individual re-breathes his own expired air, and does not cease respiratory movements, it is found that a much higher percentage can be tolerated; indeed, in some determined persons, unconsciousness may occur first. The cause of this is not quite certain, but it seems that holding the breath causes much greater oxygen lack to the tissues than re-breathing, because the circulation is impeded by the loss of the respiratory pump.

Cheyne-Stokes Respiration.

This is a condition in which the breathing waxes and wanes (fig. 116). It is an exaggeration of the type of respiration which is often seen during sleep in perfectly healthy people. It may be induced in normal persons if they make themselves pant violently for 1-2 minutes. If then respiration is allowed to take its own course, there will first be a pause (apnoea), then Cheyne-Stokes respiration will be set up. The groups will become less and less distinct, and respiration will ultimately become normal. The explanation is as follows:—

The panting causes an undue amount of carbonic acid to be swept out of the body, with the result that the carbonic acid tension in the blood and in the tissues sinks to perhaps a quarter or a third of its usual value. Already we have seen that carbonic acid is an

active stimulant to the respiratory centre, and its removal causes respiration to cease, hence the apnoea. But during the apnoeic period the arterial blood becomes less and less oxygenated. This causes the respiratory centre to become unduly irritable, so that when carbon dioxide does accumulate it over-stimulates the centre and causes itself to be washed out again; another period of apnoea or of reduced respiration is then produced. Cheyne-Stokes breathing appears to be dependent on oxygen-want, but there are many other factors concerned in its production.

It has been shown for example that the production of such periodic respiration is easier if the body is cooled, when the subject is lying down, or is rested before the overventilation. A cuff placed on the limbs to block the veins and thus withdraw blood from the circulation increases respiratory periodicity (J. N. Mills). It is suggested that pulmonary congestion may play a part.

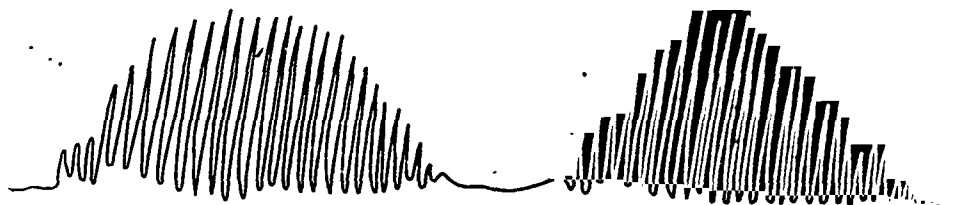


FIG. 116.—Stethograph tracing of Cheyne-Stokes respiration in a man. The time is marked in seconds. (Pembrey and Allen.)

“If from any cause, such as cerebral hæmorrhage or circulatory failure, the circulation through the respiratory centre is interfered with, or if the absorption of oxygen is interfered with by such causes as diminished barometric pressure or pathological conditions in the lungs, the occurrence of periodic or Cheyne-Stokes breathing becomes easily intelligible.”—(Haldane and Douglas.)

Researches by Roberts and by Mellanby and Huggett seem to show the presence of vasomotor changes in the medulla which cannot be ignored as a factor in Cheyne-Stokes respiration.

Pathological Cheyne-Stokes respiration may be removed by administration either of oxygen or of carbonic acid, but sometimes it is unaffected by breathing oxygen (J. N. Mills).

It is not, however, to be presumed that Cheyne-Stokes respiration is necessarily a pathological state. It occurs in many normal persons during sleep.

The Effects of Exercise on Respiration.

We are all familiar with the fact that physical exercise increases the rate of respiration. This is due to a variety of causes which are of the greatest importance in medicine. The first two we have already considered.

1. An accumulation of carbon dioxide and lactic acid in the blood.
2. Oxygen-want acting on the aortic and carotid bodies.
3. Inadequacy of the circulation. It is a little difficult to decide how this cause acts normally, but its importance is made very evident by well-known observations that breathlessness is a common symptom of heart disease, especially when the mitral valve is affected and the symptom is markedly increased by exercise. In most cases blood accumulates in the lungs as shown by a diminution of the vital capacity, in others the increase of breathing may be caused reflexly. An adequate speed of circulation permitting the accumulation of carbon dioxide or oxygen lack in the arterial blood does not seem to be of anything but theoretical importance for the blood is usually over-aerated.

All these factors may be accentuated by (1) lack of training, which results in a poor performance of the heart and uneconomical methods of doing work, with the result that larger amounts of muscle are used than are necessary. This is well seen in the breathlessness produced in the fat or old man laboriously climbing, compared with the ease with which a young athlete can run up stairs. Therefore, when the heart is fatty or actually diseased the breathlessness of exercise tends to be increased. It seems that the inadequacy of the heart allows the accumulation of blood in the lungs and a marked reduction of the vital capacity, and therefore of the gaseous exchanges in the lungs. (2) Lack of hæmoglobin, or fixation by carbon monoxide, by reducing the gas-carrying power of the blood similarly increases the effect of the exercise.

The higher centres play an important part in the increase of respiration, which takes place at the very beginning of, or even before, exercise. Mere emotion may be sufficient to cause a marked over-ventilation, which may even result in tetany if the subject is deficient in calcium.

Special Respiratory Acts.

Coughing.—In the act of coughing there is first of all a deep inspiration, followed by an expiration; but the latter, instead of being easy and uninterrupted, as in normal breathing, is obstructed; the glottis being momentarily closed by the approximation of the vocal cords. The abdominal muscles, then acting strongly, push up the

viscera against the diaphragm, and thus make pressure on the air in the lungs until its tension is sufficient to open noisily the vocal cords which oppose its outward passage. In this way considerable force is exercised, and mucus or any other matter that may need expulsion from the air-passages is quickly and sharply expelled by the out-streaming current of air. The act is a reflex one, the sensory surface which is excited being the mucous membrane of the larynx, and the superior laryngeal nerve is the afferent nerve; stimulation of other parts of the respiratory mucous membrane will also produce cough, and the point of bifurcation of the trachea is specially sensitive. Other sensory surfaces may also act as the "*signal surface*" for a cough. Thus, a cold draught on the skin, or tickling the external auditory meatus, in some people will set up a cough.

Sneezing.—The same remarks that apply to coughing are almost exactly applicable to the act of sneezing; but, in this instance, the blast of air, on escaping from the lungs, is directed, by a contraction of the pillars of the fauces and descent of the soft palate, chiefly through the nose, and any offending matter is thence expelled.

The "*signal surface*" is usually the nasal mucous membrane, but here, as in coughing, other causes (such as a bright light) will sometimes set the reflex going.

Hiccough is an involuntary sudden contraction of the diaphragm, causing an inspiration which is suddenly arrested by the closure of the glottis, causing a characteristic sound. It usually arises from gastric irritation.

Snoring is due to vibration of the soft palate.

Sobbing consists of a series of convulsive inspirations at the moment of which the glottis is partially closed.

Sighing and *Yawning* are emotional forms of inspiration, the latter associated with stretching movements of jaws and limbs. They appear to be efforts of the nervous system to correct, by an extra deep inspiration, the venosity of the blood due to inactivity produced by ennui or grief.

There are many other abnormalities of the respiratory mechanism which will become familiar to the student of medicine during his clinical studies. We may mention, as an example, *laryngismus stridulus* (the spasmodic croup of children). This is a nervous affection due to increased reflex irritability of the laryngeal mechanism; the fits of suffocation are produced by tonic spasm of the adductor muscles of the glottis, such as may occur in rickets and which really is a laryngeal manifestation of tetany.

Artificial Respiration.

In experiments on animals in which it is necessary to open the chest, life can be maintained by pumping air into the lungs; this is done by means of some form of pump or bellows, the delivery tube of which is connected to the trachea by a cannula, a side hole in which provides for the escape of the expired air. A bottle containing the anæsthetic may be placed on the course of the delivery tube.

Artificial respiration is sometimes necessary in man to restore normal breathing, as for instance in those who are apparently dead from drowning. In such cases speed in commencing the artificial breathing, and perseverance in continuing the process are essential. Many have been restored to life after the efforts have been continued



A



B

FIG. 116a.—This illustrates the two principal positions A and B in performing Schafer's method of artificial respiration. Reproduced by permission of Sir E. Sharpey-Schafer and the National Life Saving Society.

for an hour or more. It is now recognised that of the numerous methods for performing artificial respiration, that introduced by Sharpey-Schafer is simple, not injurious, and very effective. He was Professor of Physiology at University College, London, and subsequently at Edinburgh. The subject is laid on the ground in the prone position, with a thick folded garment under his chest. This position facilitates the flow of water from the mouth which should be freed of all obstructions, mud, weeds, etc. The operator kneels by his side or athwart him facing his head, and places his hands on the small of the patient's back. He slowly throws the weight of his body forwards, and thus presses upon the abdomen of the subject, and forces air out of the lungs; he then gradually relaxes the pressure by bringing his body up again, but without removing his hands. Sharpey-Schafer insisted on the point that the driving upwards of the diaphragm by the pressure on the abdomen is more important than attempting to push up the ribs. This is repeated regularly at the rate of twelve to fifteen times a minute until normal respiration begins, or until all hope of restoration is given up, but while the heart beats there is hope.*

It cannot, however, be over-emphasised that the important thing about artificial respiration is to **get begun**, for every second's delay makes recovery less likely. On the operating table during a surgical operation it may not be convenient to turn the patient on his face, but adequate respiration may be obtained by gentle rhythmical compression of the abdomen or by pulling up the ribs by means of the arms (Sylvester's method). Almost any method gives a ventilation equivalent to the normal tidal air.

Mechanical Artificial Respiration.

The prevalence of anterior poliomyelitis (infantile paralysis), which may lead to paralysis of the medulla, has necessitated the introduction of a variety of mechanical methods by which artificial respiration may be continued for prolonged periods. The chief method in use is that of Drinker, in which the patient's chest and abdomen are enclosed in an airtight chamber in which a negative pressure can be produced rhythmically. In the Bragg-Paul method the chest is rhythmically compressed by inflating a bag fastened round it.

Ventilation.

Some observers have stated that certain noxious substances are ordinarily contained in expired air which are much more poisonous than carbonic acid, but careful research has failed to substantiate

* Recently a rocking method has been introduced by Eve, but requires the use of a stretcher. It is stated to bring about a greater oxygen uptake than Schafer's method) Hemingway, 1944).

this view. If precautions be taken by absolute cleanliness to prevent admixture of the air with exhalations from skin, teeth, and clothes, the expired air contains only one noxious substance, and that is carbonic acid.

An adult gives off about 0.6 cubic feet of carbonic acid per hour, and if he is supplied with 1000 cubic feet of fresh air per hour, he will add 0.6 to the 0.4 cubic feet of carbonic acid it already contains; in other words, the percentage of that gas will be raised to 0.1. An hourly supply of 2000 cubic feet of fresh air will lower the percentage of carbonic acid to 0.07, and of 3000 cubic feet to 0.06, and this is the supply which is usually recommended. In order that the air may be renewed without giving rise to draughts, each adult should be allotted sufficient space in a room, at least 1000 cubic feet, but this is seldom possible.

Leonard Hill considers that since the carbon dioxide even of a stuffy room seldom rises above 0.1 per cent., a level which is readily compensated by an imperceptible increase in respiration, the effects of bad ventilation are not so much due to changes in the chemical composition of the air, as to the absence of movement in the air; moving air has a stimulating, and still hot air a depressing effect.

Air Raid Shelters, etc.

In war time the length of time an air-tight room can be occupied safely is of considerable practical importance. By experiment on man Haldane has found that such a room may be occupied until the oxygen has fallen to 14 per cent., that is with carbon dioxide also accumulating to about 6 per cent. This means that one person at rest can safely occupy a room of 25 cubic feet for two hours. For convenience it may be noted that 1 cubic foot contains 28.3 litres.

CHAPTER XIX

THE RELATION OF RESPIRATION TO OTHER PROCESSES IN THE BODY

The Effect of the Respiratory Movements on the Circulation and the Pulmonary Circulation.

THE main effect of respiration on the circulation is shown in the accompanying figure (fig. 117). It will be noticed that the arterial pressure rises with inspiration and falls with expiration, but that

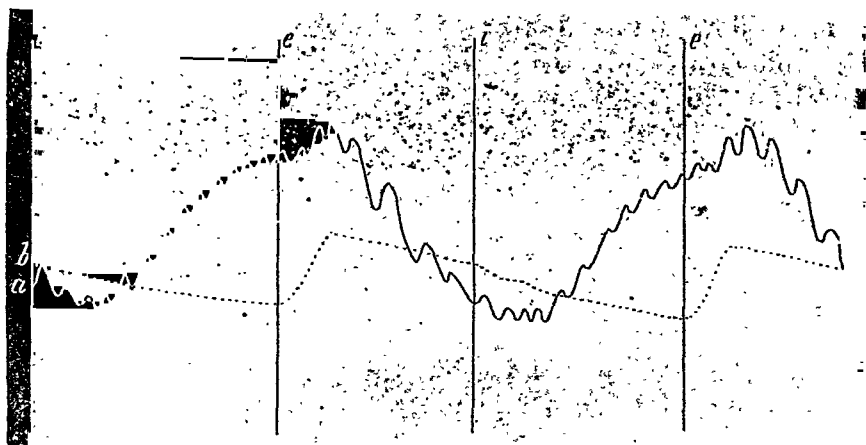


FIG. 117.—Comparison of blood-pressure curve with curve of intra-thoracic pressure. (To be read from left to right.) *a* is the curve of blood-pressure with its respiratory undulations, the slower heart-beats on the descent being unusually well marked; *b* is the curve of intra-thoracic pressure obtained by connecting one limb of a manometer with the pleural cavity. Inspiration begins at *i* and expiration at *e*. (M. Foster.)

the two events are not quite synchronous, the rise of pressure beginning a little later than the inspiratory act, and the fall a little later than the expiratory act.

These variations are chiefly the result of the mechanical conditions dependent on the lungs and heart with its large vessels being contained within the air-tight thorax. If the **intra-thoracic pressure** is measured, it is found that it varies from -5 to -7 mm. of mercury at the end of expiration to -30 at the end of a deep inspiration; that is to say, from 5 to 7 to 30 mm. less than the

atmospheric pressure (760 mm. of mercury). The pressure outside the heart and the thoracic vessels is correspondingly diminished during inspiration to the same extent, and produces its main effect (distension) upon the thin-walled veins and the right heart and pulmonary circulation. At the same time there is a diminished resistance in the pulmonary circuit (Sharpey-Schafer), and lowered pressure in the pericardium (Lewis) and this allows the heart to fill more easily. When the chest cavity is enlarged in inspiration, not only is air sucked into the lungs but more blood is also sucked into the veins and so into the heart. In expiration the reverse occurs. This causes a momentary reduction of the amount of blood which reaches the left side of the heart and a slight fall of blood-pressure, but after a few beats this is more than compensated for by an increased flow due to the reduced resistance of the pulmonary circuit and increased output of the right side of the heart. During expiration the pressure in the lungs rises for there is considerable resistance to the exit of air. When the lung is compressed, the blood it contains can, because of the pulmonary valve, only flow forward towards the left side of the heart, and the blood-pressure rises momentarily, but by the middle of expiration the pulmonary resistance is so increased and the amount of blood entering the chest so reduced that the blood-pressure falls.

Various other factors are also concerned. During inspiration there is an irradiation of impulses to inhibit the vagus centre causing the heart to go fast. In some persons this is quite marked and is known as *sinus arrhythmia*.

The effect of inspiration on arterial blood-pressure is at first assisted by the pressure of the diaphragm, as it descends, on the abdominal veins, and blood is thus sent upwards into the chest by the vena cava inferior. On the other hand, this is to some extent counterbalanced by the obstruction in the passage of the blood downwards in the abdominal aorta, but again the veins are the vessels more easily influenced by moderate changes in external pressure.

All these changes are naturally best seen when respiration is slow and deep; this may be done voluntarily or in animals by cutting the vagi or cooling the medulla. They are of considerable importance in the return of the venous blood from the lower part of the body while in the erect posture and constitute what is known as the **Respiratory Pump**.

Artificial respiration performed by means of a pump which forces air into the chest produces converse undulations in blood-pressure; each blast of the pump increases the pressure in the lungs and in the chest and causes a reduction in the output of the heart, like the normal expiratory act.

Valsalva's Experiment.—In speaking of the effects of expiration, we have considered only ordinary quiet expiration. With forced expiration, there is considerable impediment to the circulation; this is markedly seen in what is called Valsalva's experiment. This consists in making a forced expiratory effort with the mouth and nose shut; the effects are most marked in people with an easily compressible thorax. By such an act the intra-thoracic and abdominal pressures rise so greatly that the outlets of the veins of the limbs, head, and neck into the thorax are blocked. At first, the blood in the lungs is forced out; this produces a slight rise of arterial pressure; but soon, if the effort is continued, the lungs are emptied of blood, the filling of the right heart is opposed, and the blood is dammed back in the peripheral veins, where the pressure rises to the mean arterial pressure. The arterial pressure begins then to fall; but before any considerable fall occurs, the expiratory effort ceases from exhaustion of the experimenter, and a deep inspiration is taken. During this inspiration, the blood delivered by the right heart is all used in the filling of the comparatively empty pulmonary vessels; thus several beats of the left ventricle become abortive, and produce no effect on the systemic arteries; the face blanches, and the subject becomes faint from cerebral anæmia. The alteration of the pulse which occurs in Valsalva's experiment may be shown graphically by the sphygmograph.

The Experimental Study of the Pulmonary Circulation.—Many of the above facts have been made out from a direct study of the pulmonary circulation. This is more difficult than that of the general circulation because of the necessity for opening the chest, and of maintaining artificial respiration.

Pressures taken in branches of the pulmonary artery are about one-third of that in the aorta, as perhaps might be expected from the thinness of the muscle of the right ventricle compared with that of the left. It has been possible to close the chest and make it airtight with a cannula in the artery, and it has been found (Sharpey-Schafer) that the pulmonary arterial pressure falls at each inspiration and rises at each expiration. If the chest is open and artificial respiration maintained by means of a pump or bellows, the rise takes place during the inflation period when the pulmonary capillaries are compressed.

There is evidence that during quiet breathing, when some of the alveoli are not in use, some of the pulmonary capillaries are closed because after an inflation of the lungs the pulmonary pressure is lower than before.

The vessels of the lungs are under nervous control like all the other vessels of the body. The subject has been studied of recent years, notably by Daly and by Wiggers.

Asphyxia.

Asphyxia may be produced by anything which prevents adequate aeration of the blood.* If the cause of the asphyxia is not due to the failure of respiration itself, as in damage to the medulla, the symptoms of asphyxia may be roughly divided into three stages: (1) the stage of exaggerated breathing (hyperpnœa) passing into dyspnœa; (2) the stage of convulsions; (3) the stage of exhaustion or collapse.

In the *first stage* the breathing becomes much deeper than usual, inspiration at first being especially exaggerated and prolonged. The muscles of extraordinary inspiration are called into action, and the effort to respire is laboured and painful. This is soon followed by a similar increase in the expiratory efforts, which become excessively prolonged, being aided by all the muscles of extraordinary expiration. During this stage, which lasts a varying time from a minute upwards, according as the deprivation of oxygen is sudden or gradual, the lips become blue, the eyes are prominent, and the expression intensely anxious. This stage is due to the powerful stimulation of the respiratory centre by the increasingly venous blood.

In the *second stage*, which is not marked by any distinct line of demarcation from the first, the violent expiratory efforts become convulsive, and then give way, in men and other warm-blooded animals, to general muscular convulsions, which arise from the further stimulation of the centres in brain and cord by venous blood. The convulsive stage is a short one, and lasts less than a minute.

The *third stage* is that of *exhaustion*. In it the respirations all but cease, the spasms give way to flaccidity of the muscles, there is insensibility, the conjunctivæ are insensitive and the pupils are widely dilated. Every now and then a prolonged sighing inspiration takes place, at longer and longer intervals, until breathing ceases altogether, and death ensues. During this stage the pulse is scarcely to be felt, but the heart may beat for some time after the respiration has stopped. The condition is due to the gradual paralysis of the centres by the prolonged action of the venous blood. This stage may last three minutes and upwards.

The changes which occur in the circulation are also characteristic. In anæsthetised animals the arterial and venous pressures rise above the normal during the first stage (fig. 118); this is due to stimulation of the vasomotor centre and of the sympathetic leading to cardiac acceleration which, together with the increased venous pressure, causes an increased cardiac output (Mathur). This latter feature may not, however, show if the heart has already been accelerated or if the sympathetic has been depressed by the anæsthetic. There is also no doubt a secretion of adrenaline which acts both on the heart

* Asphyxia is therefore a combination of oxygen want and excess of carbon dioxide.

and blood-vessels. If the vagi are not divided previously, the rise of pressure is much less, and as the asphyxia proceeds the cardiac



FIG. 118.—Tracing of asphyxia from a curarised and anaesthetised cat; artificial respiration ceased at about the third time marking from the left. The upper tracing (A) is that of the arterial pressure, taken with a mercurial manometer. The lower tracing (V), which at first indicates negative pressure, is that of the venous pressure taken with a salt solution manometer. (By Sir C. J. Martin.)

acceleration is replaced by cardiac slowing: this enables the heart to last longer, and is due to excitation of the cardio-inhibitory centre by venous blood. The final fall of blood-pressure is due to cardiac failure and to the dilator effects of carbon dioxide and other substances such as histamine and adenosine triphosphate which may be

liberated on the internal peripheral vessels. Later the vasomotor centre dies.

It should be noted that similar central effects are produced by asphyxia of the head only, even if artificial respiration is kept up. The late slowing of the heart is an important diagnostic sign of asphyxia of the brain in cerebral injuries.

After death the right side of the heart and the great veins are engorged with venous blood, while the left side and the arteries are empty. This is the result of the failure of the heart as a pump, and of the contraction of the smaller arteries and skin capillaries which together cause the enormous rise in venous pressure.

The Relation of Respiration to Nutrition.

The gaseous interchanges in the lungs constitute what is frequently termed *external respiration*. Oxygen obtains an entrance into the blood, and is carried to the tissues in the loose compound known as oxyhæmoglobin. In the tissues, this compound is dissociated, and the respiratory oxygen is utilised by the tissue elements for the combustion processes which occur consequent on their activity. Of the ultimate products, carbonic acid and a portion of the water find an outlet by the lungs, to which they are transported by the venous blood. The gaseous interchanges in the tissues constitute what is known as *internal* or *tissue respiration*.

Tissue Respiration.—External or pulmonary respiration is much less obscure than tissue or internal respiration. It must be borne in mind, however, that pulmonary respiration is but the means, and tissue respiration is the end.

Tissue respiration consists in the passage of oxygen from the blood of the capillaries to the cells of the tissues, and the passage of carbonic acid in the reverse direction. This gaseous interchange is no doubt brought about by a simple process of diffusion. The

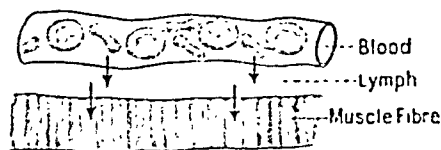


FIG. 119.

oxygen passes out of the plasma of the blood through the capillary wall, and then through the lymph until it reaches the cell in which it is to be used, which we will suppose is a muscle-fibre (fig. 119). In order that a constant stream of oxygen may pass

from the blood to the fibre, there must be a difference of oxygen pressure between the oxygen dissolved in the plasma, and that dissolved in the lymph, and the latter must be at a greater pressure than that dissolved in the muscle-fibre. The amount of oxygen which passes will, other things being equal, be directly

proportional to these pressure differences, and as the amount varies greatly at different times, it is obvious that the pressure differences also vary greatly. When the muscle is at rest, the oxygen pressure in the capillaries is very near to that in the muscle-fibre; when the muscle is active and using large quantities of oxygen, the intra muscular oxygen is reduced and more oxygen enters the muscle.

The tension of oxygen in tissue lymph has been investigated by injecting a bubble of nitrogen into the tissue spaces or body cavities, and subsequently withdrawing and analysing the bubble after equilibrium has become established between the gases in the bubble and in the lymph. The tensions of oxygen thus obtained usually vary between 20 and 40 mm. Hg., with an increase up to 70 mm. during increased blood supply or some decrease below 20 mm. during decrease of blood supply or during increased use of oxygen when there is increased tissue activity. The oxygen tensions within the cells bathed by the lymph are probably similar to those in the lymph with the possibility of some variation in different parts

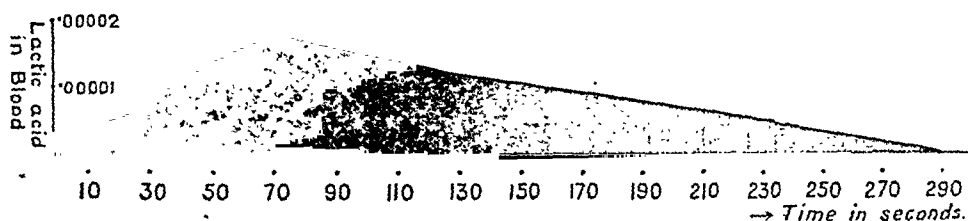


FIG. 120.—The black area represents the lactic acid thrown into the blood during the time following a tetanus that lasted 84 seconds; the work done by the muscle was 70 gramme-centimetres; the total quantity of lactic acid formed was 0.003 gramme. The figures on the vertical line represent fractions of a gramme of lactic acid per second.

of the cell. Thus in muscular activity lactic acid may be formed in certain parts of the fibre at a more rapid rate than oxygen can diffuse to these parts. It is likely that the more vital parts, *e.g.* nuclei of cells of an aerobic organism like man, are normally never without oxygen (Argyll Campbell).

From what has been said regarding the effect of carbon dioxide and acids in reducing the amount of oxygen held by the blood it may be deduced that the capillary oxygen pressure will be raised by the increased quantity of acid which is thrown into the blood as the result of muscular activity. The above diagram (fig. 120) shows the extent, both in degree and time, of this pouring of acid into the blood as the result of a short tetanic contraction of a muscle.

In glandular structures the oxygen pressure is higher than in muscle; probably owing to the relatively more copious blood-supply of glands, equilibrium is more readily established between the blood and the gland cells, the oxygen pressure in the cells being almost that present in venous blood.

The quantity of oxygen used by different tissues varies not only

with the degree of their activity, but also with the nature of the tissues. On the whole it may be said that, weight for weight, glandular tissue uses most oxygen; next in order come the muscular tissues, and last of all, the connective tissues. There are some important tissues, notably the nervous system, about which little is known in this connection. The amount of oxygen used by an organ or tissue per gramme per minute is called its *coefficient of oxidation*, which is calculated after weighing the organ, ascertaining the amount of blood which flows through it in a given time, and by finding the difference in oxygen content of the blood arriving at and leaving the tissue.

Relation of Tissue Respiration to Functional Activity.—In all organs increased activity is accompanied by increased oxidation.

Much interest is centred in the question of the order of time in which these events take place. The matter has been investigated in skeletal muscle and in the submaxillary gland (fig. 121), both

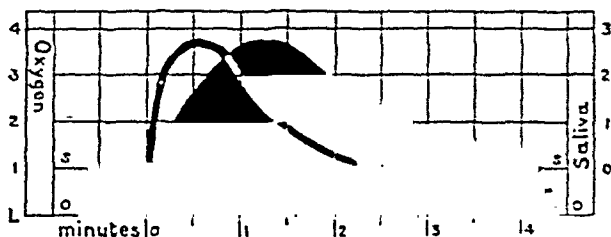


FIG. 121.—The black-white line represents rate of salivary secretion in c.c. per minute. S—S=base line for saliva. Black area=oxygen used by the gland. O—O=oxygen base line.

of which organs can be thrown into profound activity for a short space of time; in each, most of the oxidation follows on the activity, and not the activity on the oxidation. The important inference is drawn that neither the contraction nor the secretion is caused by the oxidation in the sense that the machinery of a locomotive is driven by the energy derived from the oxidation of the coal; rather is the mechanism like that of a spring which is liberated at the moment of doing the work, and has to be rewound subsequently; the process of rewinding involves oxidation (see Muscle). In muscle we have seen that the heat-formation which occurs in the period following activity takes place only if the muscle is supplied with oxygen. The output of carbonic acid, in its turn, follows the intake of oxygen. The order of events is therefore: (1) increase of functional activity; (2) increase of heat formation and oxygen taken in; and (3) increase of carbonic acid output.

The table on p. 251 shows the coefficients of oxidation for resting organs, and the extent to which they are increased in activity. In many cases the quantitative relationships have not been worked out.

It has been shown on the heart that if N is the number of beats per minute, T the maximum blood-pressure which is attained at each beat, and O the amount of oxygen used; then $\frac{N \times T}{O}$ is a constant quantity, unless the cardiac muscle is itself rendered less efficient, as may be done by the use of drugs. This is in agreement with a series of researches on the heat given out by frog's muscle, which shows that the heat given out in a single contraction varies directly with the tension in the muscle. In other words, the amount of oxygen used and heat evolved is, as might be expected, proportional to the work done by the tissue as shown by the following table. The student should read the section on the Chemical Changes in Muscle at this stage.

Organ.	Condition of Rest.	Oxygen used per minute per gramme of organ.	Condition of Activity.	Oxygen used per minute per gramme of organ.
Voluntary muscle.	Nerves cut. Tone absent.	0.003 c.c.	Tone existing in rest. Gentle contraction. Active contraction.	0.006 c.c. 0.020 c.c. 0.080 c.c.
Unstriated muscle.	Resting.	0.004 c.c.	Contracting.	0.007 c.c.
Heart.	Very slow and feeble contractions.	0.007 c.c.	Normal contraction. Very active.	0.05 c.c. 0.08 c.c.
Submaxillary gland.	Nerves cut.	0.03 c.c.	Chorda stimulation.	0.10 c.c.

The Mechanism of Oxidation.

Many students may prefer to defer reading this section until they have completed Intermediate Metabolism.

The oxidation of foodstuffs is, unfortunately, not so simple as the oxidation of metals. None of the carbohydrates are oxidised by merely exposing them to oxygen, yet they are easily oxidised in the body. It is evident that some catalytic process is necessary. The whole mechanism has now been shown to depend on the existence of a large number of organic catalysts or enzymes, which may catalyse both oxidation and reduction.

The first step in the study of the processes concerned was the discovery of *oxidases* or oxygen-carriers. If the resin guaiacum is exposed to air it is unaffected, but if a plant juice such as that

of potato is added it becomes dark blue. If now alcohol is added to such juice a precipitate is formed which will not act like oxidase but will cause the guaiac to be oxidised only in the presence of hydrogen peroxide. It was subsequently found that the plant juice contains phenolic substances which are auto-oxidisable and form organic peroxides from which oxygen is readily available for activation and use by *peroxidases*. It is the oxidation of these auto-oxidisable substances to organic peroxides which causes the rapid darkening of a cut apple or potato exposed to air. Ferrous salts generally have the power of acting as peroxidases and cause a large number of reactions similar to those which occur in the body, such as the oxidation of fatty acids (see later page) and of glucose to glucuronic acid. The hæmoglobin of blood also has a peroxidase-like action and its presence can be demonstrated by adding to it hydrogen peroxide and guaiac. This, indeed, is a recognised test for blood.

Oxidation does not necessarily involve the addition of oxygen. A simple chemical equation indicates that the taking up of hydrogen comes to the same thing. Thus in $\text{HO}_2 + \text{H}_2 = 2\text{H}_2\text{O}$ we can look upon the hydrogen as being oxidised, on the peroxide as taking up hydrogen.

In tissues and fluids this subject has been studied by the use of methylene blue which is colourless when hydrogen is added to it. If this dye is brought into contact with living tissue it becomes decolorised, and as this occurs in the absence of oxygen, and as methylene blue is not an oxidising agent in the ordinary sense, it may be presumed that it takes up hydrogen.

On further investigation it has been found that the decolorisation depends on an enzyme which has been called *dehydrogenase* which transfers the hydrogen to the hydrogen acceptor, in the above case the methylene blue. Further, it becomes evident if the now reduced acceptor, with its extra hydrogen, was allowed to take up O_2 , it may produce either water or hydrogen peroxide. But hydrogen peroxide is harmful to tissues, and we are therefore not surprised to find that there exists in tissues still another enzyme *catalase*, which rapidly breaks it up to form water releasing oxygen. It is, indeed, for this reason that the oxygen bubbles off from hydrogen peroxide in contact with tissues. It should, however, be noted that a catalase differs from a peroxidase in that the latter activates hydrogen peroxide without decomposing it.

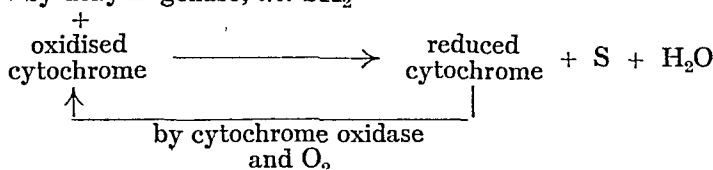
In the tissues it has now become apparent that the processes of oxidation and hydrogen acceptance both occur and that there exist a number of substances which are alternately oxidised and reduced. Such catalytic substances are the iron containing pigments *cytochromes* and the tripeptide *glutathione*. There is present also in tissue a *yellow oxidation catalyst*, a complex flavin, which appears to act like methylene blue and to be related to the activities of vitamins B_2 and possibly C.

Some of the tissue poisons like cyanide and anæsthetics act by interfering with the enzyme actions concerned in the tissue oxidation.

Of the catalysts the cytochrome system seems to be the most important. Cytochrome, of which there are several varieties, is a hæmochromogen related to the blood pigments. It acts as a hydrogen carrier but is not itself oxidised.

If we take the cytochrome system as an example we see that the substance acted upon first has its hydrogens activated and we may call it SH_2 , in which form it is easily oxidised by the oxidised cytochrome. The latter becomes reduced but is again reoxidised by oxygen in the presence of another enzyme, cytochrome oxidase (formerly called indophenol oxidase because of the test for it). The reaction may be shown thus:—

Substance to be acted upon
activated by dehydrogenase, *i.e.* SH_2



The whole subject is admittedly extremely complex and much research on it has yet to be done.

The Total Gaseous Exchange.—This depends entirely on the needs of the body, and, as pointed out by Haldane, it is important to remark that the muscles control respiration just as they do the circulation and arrange, largely by virtue of the carbon dioxide and lactic acid they produce, that their needs are provided for. In each instance their requirements may be anticipated by the effect of the higher centres, but this is not essential.

At rest the oxygen intake of an average man is 200-400 c.c. per min., but this varies according to the work done and many other factors. (See Basal Metabolism.)

The Respiratory Quotient.—This is the ratio between the volume of carbon dioxide given out and the volume of oxygen retained, *i.e.* $\frac{\text{CO}_2}{\text{O}_2}$. The amounts of these gases in the expired air and inspired air are seen in the following table, which gives average figures:—

	Inspired Air.	Expired Air.
Oxygen . . .	20·96 vols. per cent.	16·03 vols. per cent.
Nitrogen . . .	79 " "	79·57 " "
Carbonic acid . . .	0·04 " "	4·4 " "
Water vapour . . .	variable	saturated
Temperature . . .	"	that of body (37° C.)

It is seen that about 5 volumes of oxygen have been taken up while 4.5 volumes of carbon dioxide have been given off. In this instance the respiratory quotient is 0.9, but the figure may vary somewhat according to circumstance.

If carbohydrate only is being burnt in the body, *e.g.* glucose ($C_6H_{12}O_6$), all the oxygen taken in appears as carbon dioxide (CO_2) in the expired air, since the carbohydrate itself contains sufficient oxygen to oxidise its own hydrogen. The respiratory quotient is therefore 1.0.

If, however, fat is burnt, *e.g.* tristearin ($C_{57}H_{110}O_6$), oxygen is also necessary to oxidise the hydrogen to water (H_2O). Thus the amount of oxygen retained becomes relatively larger than that of the carbon dioxide expired—and the respiratory quotient becomes less than unity. The respiratory quotient may therefore be used to indicate the relative amounts of fat and carbohydrate which are being used as fuel in the body. Protein gives a respiratory quotient of about 0.82, *i.e.* between fat (0.7) and carbohydrate (1.0), and therefore does not influence the total respiratory quotient appreciably.

In the above table the nitrogen content of the sample of air is obtained by subtracting the amount of $O + CO_2$ from 100, but for reasons just given the $O + CO_2$ expired is not equal to the amount inspired, and the amount of nitrogen expired appears larger than that inspired. In more accurate work this is taken account of, and the actual amount of oxygen inspired for each 100 c.c. of air expired is found thus: $20.96 \times \frac{79.57}{79}$. This divided into the CO_2 expired is known as the *corrected respiratory quotient*.

Oxygen Debt.—During severe exercise it is impossible for an individual to take in as much oxygen as is needed for the exercise, and, as we have already seen in relation to the chemistry of muscular contraction an oxygen debt is contracted. Lactic acid is produced and lactates are formed by its action on the bicarbonates. After the exercise the debt gets repaid, the lactates becoming oxidised. This shows itself by the increased oxygen consumption which continues for a considerable period after the exercise has ceased (see fig. 26, p. 42). Thus we see that the facts which have been found in relation to isolated muscle apply also to the body as a whole.

The Effect of Exercise on the Respiratory Quotient.—During severe exercise it is found that the respiratory quotient may rise above unity. This is considered to be due to excessive stimulation of the respiratory centre by afferent impulses and partially to carbon dioxide being liberated from the bicarbonate of the blood by lactic acid. When the exercise ceases the respiratory quotient rises abruptly and may even reach 2 as a result of the cessation of the hyperpnœa. Gradually, however, the opposite state of affairs occurs. The lactate in the blood gradually undergoes oxidation during the recovery and alkali is set free. Carbon dioxide is now retained to form bicarbonate so to maintain the acid-base equilibrium of the blood and the respiratory quotient falls below 1.

Hill, Long, and Lupton have collected the expired air during the exercise and the recovery period, and it has been found that the respiratory quotient for the total

excess metabolism of exercise is exactly unity, a fact which goes to indicate that in exercise carbohydrate is the fuel used. In prolonged exercise a fall in this respiratory quotient suggests the use of fat.

Local Oxygen-Want.

This may occur if there is obstruction to the blood-supply of or venous return from an organ. If due to arterial obstruction or to simple pressure, gangrene or death of the part rapidly ensues unless collateral circulation is established; if due to venous obstruction, the vitality is impaired and, until the blood has found some other route of return, marked swelling of the part, as the result of increased permeability of the impaired capillaries, is evident.

General Oxygen-Want.

Barcroft in describing the methods by which oxygen-want may be produced has adopted a homely simile. He compares oxygen-want to failure of the milk supply. It may be due to three causes: 1. There may not be enough milk at the dairy. 2. The milk may be adulterated so that what is sold is not milk. 3. The milkman may not call. In 1, the anoxic type, the blood is normal but does not take up sufficient oxygen in the lungs. Usually this is due to failure of the respiratory mechanism. In 2, the anæmic type, the blood is deficient in hæmoglobin and cannot carry oxygen. This occurs in coal-gas poisoning and in anæmia. In 3, the stagnant type, there is faulty transport of normal blood which may contain the normal amount of oxygen. This variety is due to a failure in the circulation.

Each of these varieties is met with in patients and usually leads to breathlessness if the fault is not due primarily to failure of the respiratory centre. The treatment of general anoxæmia is, however, of great practical importance as the condition rapidly leads to tissue destruction and death if allowed to persist.

One of the most dramatic varieties of oxygen-want is that produced when a man descends into a well filled with gas which is not of itself harmful. The onset of unconsciousness is sudden and without warning, exactly as occurs when the blood-supply to the brain is cut off. The breathing of pure nitrogen or any gas other than oxygen produces a similar result. In ascent to a high altitude the onset of the oxygen-want is more gradual (see below).

Breathlessness or Dyspnœa may be produced by one or both of two causes:—(1) Increase in the stimuli which play on the respiratory centre, and (2) Increase in the irritability of the centre itself. The respiratory centre does not escape the influence

of drugs which exalt or depress the excitability of the medulla. Anæsthetics and narcotics depress respiration while analeptics stimulate it.

The commonest cause of dyspnœa is exercise, which increases the amount of CO_2 in the blood, but increased respiratory activity like increased heart rate may precede the exercise through the effect of the higher centres. In sustained or severe exercise the effect of CO_2 is enhanced by the production of lactic acid. If the exercise is prolonged the well-known phenomenon of **second wind** occurs. This appears to be in part the result of a more economical use of the muscles and the lessened production of carbon dioxide since it has been found that at this stage there is a fall in the alveolar CO_2 . By this time the circulation has also adapted itself to its task.

It is important to remark that anything which causes delay of the circulation also causes increased respiration since it is improbable that delay of blood-flow through the brain stimulates respiration; certainly it cannot be produced experimentally. Presumably the paralysing effect of the oxygen want on the centres more than counteracts, blood tends to accumulate in the lungs, the vital capacity is decreased and the exchange of gas in the lungs is mechanically interfered with. This occurs in some forms of cardiac disease.

Breathlessness, it will be evident, is brought about by anything which reduces the respiratory quality of the blood, such as blood loss or the presence of abnormal acids, or by anything which causes faulty oxygenation of blood in the lungs. Whenever there is present any pathological state which tends to produce breathlessness, this symptom is increased by exercise.

The extent, however, to which exercise will produce dyspnœa depends on training which makes it possible for the exercise to be carried out with greater economy.

Respiration at High Pressures.

Prolonged exposure to pressures of oxygen, equal to 1300 to 1400 mm. of mercury, induces pneumonia, and death rapidly follows. It is not possible, therefore, for men to work in air which is compressed to the extent of producing so great a pressure of oxygen.

Caisson Disease.—In work under water it is usual to sink an iron bell or caisson in which the men work and from which the water is excluded by pumping air in at a pressure higher than that of the water. The men enter through a chamber with double doors or "air-lock." In this chamber the pressure can be raised or lowered. The pressure in the caisson rarely exceeds 4 atmospheres, which corresponds to about 600 mm. of oxygen; at this pressure

the workers do not suffer whilst they are in the caisson, but grave symptoms may develop shortly after they have come out. Similar symptoms are experienced by divers who come to the surface from great depths. The symptoms may take the form of paralysis, vomiting, severe abdominal pain, which may cause "bends," vertigo, etc. They are due to the fact that the plasma and the tissue fluids have become saturated with oxygen and nitrogen at the pressure of the caisson, and when the pressure is suddenly removed, minute bubbles, especially of nitrogen (the oxygen being used), form throughout the body and injure such tissues as the spinal cord, or produce blockage of the vessels. Short hours are necessary for caisson workers, for then the body has not time to get saturated with air at the caisson pressure, and in all cases "decompression" must be gradual and slow; this gradual release from pressure is accomplished in the "air-lock." L. Hill, who introduced the method, advocated the use of high oxygen tension in the decompression chambers.

The effects of still higher pressures occur in the escape chambers of submarines in deep water, *i.e.* about 300 feet. At such pressures nitrogen becomes an intoxicant (Haldane).

Ascent to High Altitudes.

The advent of aircraft and the importance of high flying in war led to an increased interest in the subject, and now there are established in many places large chambers from which it is possible to pump out the air and thus produce, at ground-level, a rarefied atmosphere like that at a high altitude.

A study of the dissociation curve of oxygen at low tensions indicates that at high altitudes the blood can take up very little oxygen. At the top of Mount Everest (29,000 feet) where the barometric pressure is only 250 mm., although the atmospheric oxygen is still 21 per cent. this only represents a tension of about 50 mm., and in the alveoli the oxygen pressure is still less. Since the body at rest requires over 250 c.c. of oxygen per minute, it is evident that at such heights serious oxygen-want results and this is increased by exercise. Climbers reduce their activity to a minimum and may only have the "energy to sup strawberry jam." At high altitudes the intense cold and carriage of kit are also serious handicaps.

Mountain sickness occurs in untrained climbers at less than 10,000 feet. Vomiting may occur; often there are bad headaches, sleeplessness, absence of self-restraint, recklessness, irritability, and an inability to carry out the more complex cerebral functions, such as arithmetical calculations. The effects, indeed, are very like

those of drunkenness. Such cerebral changes have caused intrepid balloonists to continue to ascend until they died. The speed of the ascent is important. Thus those who go to the top of Pike's Peak in Colorado (14,000 feet) by rail from the lower country are more affected than those who go by stages. Those who ascend slowly show remarkable adaptation. This was well seen in the Everest expeditions.

Adaptation to high altitudes consists (1) in increased pulmonary ventilation; (2) increased heart-rate and cardiac output. A deficient supply of oxygen in the blood stimulates respiration reflexly from the carotid and aorta and so produces increased pulmonary ventilation. This increases the tension of oxygen in the alveoli.

Altitude.	Observed alveolar pressure of oxygen.	Alveolar oxygen pressure which would have existed had no adaptation taken place.
Sea-level	100 mm.	100 mm.
15,000 feet	52 "	38 "

The increased *depth* of respiration is quite evident in ordinary aeroplane ascents.

(3) The other important method of adaptation is in the increase of corpuscles and hæmoglobin, and consequently of the oxygen capacity of the blood. In consequence the oxygen tension in the tissues is increased.

	Corpuscles per c.m. in millions.	Hæmoglobin value on hæmoglobinometer scale.	Oxygen capacity of blood.
Sea-level	4.9	99	830 c.c.
After 1 week at 14,000 feet	5.4	115	870 "
" 2 " "	5.75	120	1040 "
" 3 " "	5.75	121	1060 "
" 5 " "	121	1088 "

It has been observed in animals that, in response to the call for oxygen, there is an increased activity of the bone-marrow which provides the corpuscles.

(4) *Excretion of Alkali by the Kidney.*—As a result of the increased breathing there is a reduction of the carbon dioxide in the alveolar air and consequently a fall in the carbon dioxide content of the blood. This is liable to cause a reduction in the hydrogen-ion concentration of the blood and reduce the dissociation of oxyhæmoglobin, but it is compensated for by an excretion of alkali by the kidney (see Acid Base Equilibrium).

It is then evident that considerable adaptation can occur. Indeed, in the Everest Expedition of 1924 Somervell and Smythe reached a height of 28,000 feet without using stored oxygen, a height much in excess of what might be expected from the dissociation curve. Although the climbing was not steep they took ten breaths for

each pace ahead. This shows that adaptation was really very incomplete. All the evidence from expeditions, however, indicates that man cannot live above 20,000 feet without deterioration shown in loss of weight and appetite, enfeeblement of the heart and nervous symptoms. Rabbits have been kept in a low pressure chamber corresponding to a height of 30,000 feet for 8 days, but they all developed serious degeneration of internal organs. Rats fed on a low protein diet, *e.g.* of carrots, show increased resistance (Argyll Campbell).

Training.—These facts indicate the importance of training for ascent to high altitude and of allowing sufficient time for the adaptations to take place. Experiments also indicate that it would be possible to train to some extent before commencing the ascent and to find out which individuals are most suitable.

High altitude flying has many problems which are peculiar, for the ascent or descent may be so rapid that adaptation is of little value, although some individuals can withstand altitude better than others. Compared with the ascent of mountains the essential difference is that oxygen is essential at lower levels, 15,000 feet, because there is not time for the processes of adaptation to come fully into play. For night flying, oxygen is necessary at still lower levels because the visual purple, which is so important for seeing, is particularly affected by oxygen want.

So-called stratosphere flying, which has the advantage of lowered air resistance and higher speeds, has still larger problems, for above 42,000 feet when the atmospheric pressure is only 126 mm. of mercury, the administration of pure oxygen at this pressure is insufficient. The aviators have to be enclosed, therefore, in air-tight suits or in cabins to which oxygen is supplied at a greater pressure than that outside. Similar difficulties occur in relation to supplying the aero-engines with oxygen, but these are overcome by the use of apparatus to compress the air which is drawn in. Special arrangements have also to be made to supply warmth. It seems, too, that an altitude sickness and "bends" due to sudden decompression and nitrogen release may also occur as in ascent from depths.

The facts are conveniently summarised in fig. 122, p. 260.

It should be emphasised in all rapid ascents that the administration of oxygen is essential above 15,000 feet, a fact which both aviators and climbers have been very loth to recognise largely for sporting reasons, and equally it has been shown that, provided oxygen is given, the human body can be taken as high as the aircraft can reach—at present 54,000 feet. Such heights make Mount Everest seem paltry. In concluding this section it may be remarked that flying at very high altitudes has been made possible

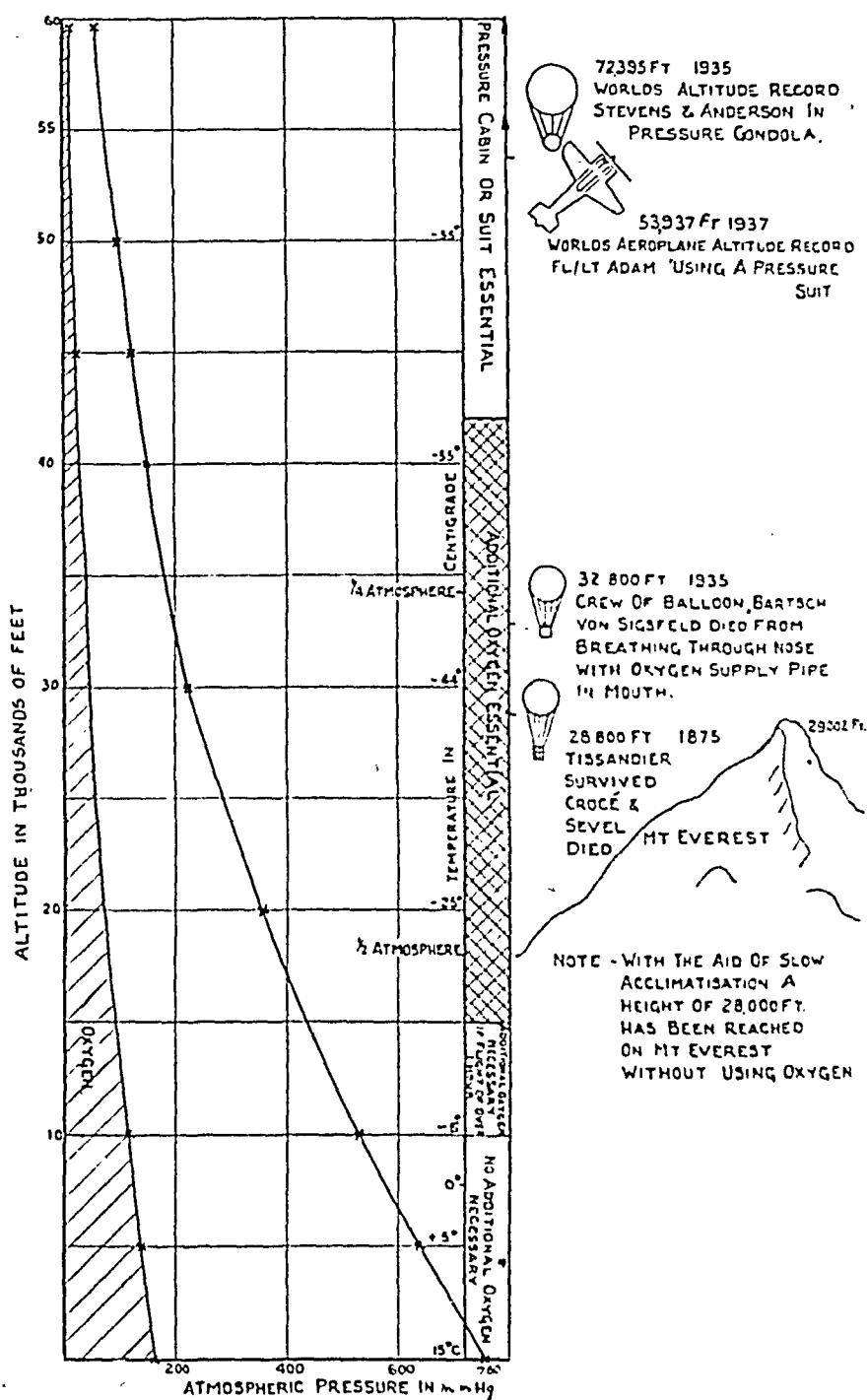


FIG. 122.—Figure showing the chief facts regarding high altitude. The aeroplane altitude record has since been raised. (By permission from the Physiological Laboratory of the Air Ministry.)

by the accurate and painstaking studies made in physiological laboratories in the interest of pure science and that even the stimulus of war has produced little new.

The Effects of Oxygen Excess.

In view of the importance of oxygen administration in high altitude flying and in respiratory disease, it may be noted that 60 per cent. oxygen can be breathed with safety for indefinite periods, but if pure oxygen is breathed, at over 1 atmosphere pneumonia may occur; there may be also faintness and convulsions. It is thought that these symptoms are caused by an insufficient reduction of hæmoglobin at rest to free sufficient base to carry away carbon dioxide, which therefore accumulates in the body.

Carbon-Monoxide Poisoning.

The fatal effects often produced by this gas (as in accidents from burning charcoal stoves in small close rooms, or where there is an escape of coal-gas) are due to its entering into combination with the hæmoglobin of the blood-corpuscles, and thus hindering their oxygen-carrying function. In an atmosphere containing both oxygen and carbon monoxide, the relative quantities of the two gases which the hæmoglobin will absorb vary with the partial pressure of the gases. The affinity of hæmoglobin for carbon monoxide is, however, 250 times that for oxygen, and the compound formed—carboxyhæmoglobin—is much more stable than oxyhæmoglobin is. If, therefore, any considerable quantity of carbon monoxide is present in the air, the hæmoglobin will be almost completely charged with carbon monoxide, and asphyxia will follow. If the patient is given pure oxygen to breathe, even at a late stage, two things will happen:—(1) The blood will take up in simple physical solution about seven times as much oxygen as when exposed to air, and this may be sufficient to carry on life; (2) as regards the saturation of the hæmoglobin, the balance is now in favour of the oxygen, relatively weak as its affinity for hæmoglobin is, and the carbon monoxide gradually becomes dissociated again and is excreted by the lungs. In treating a patient so poisoned, therefore, it is important to remove him to a good atmosphere as soon as possible. In rescue apparatus it is now common to supply 7 per cent. carbon dioxide with the oxygen. This stimulates the failing respiration (Yandell Henderson, Drinker).

CHAPTER XX

THE CHEMICAL COMPOSITION OF THE BODY

OUT of the eighty odd elements which are now known only a relatively small number are found in the bodies of the higher animals. Of these the most important are:—carbon, nitrogen, oxygen, hydrogen, sulphur, phosphorus, sodium, potassium, calcium, magnesium, iron, chlorine, iodine, with traces normally of fluorine and occasionally of manganese, copper, lead, and silver. Of these, only three are found in the free state, viz., in the blood nitrogen and to a less extent oxygen, in the intestine traces of hydrogen resulting from fermentative processes. With these exceptions the elements are present in combinations as chemical compounds of various types which are grouped by convention into—

(1) Organic compounds, *i.e.* those containing carbon.

(2) Inorganic, *i.e.* all the rest.

The naturally occurring organic compounds are grouped into carbohydrates, proteins, fats, the sterols—and other unclassified substances.

CARBOHYDRATES.

The **Carbohydrates** are found chiefly in vegetable tissues, and many of them form important foods. Some carbohydrates are, however, found in or formed by the animal organism. Among the more important carbohydrates are *starch*, *glucose*, *fructose*, and *lactose*.

They are built up in plants from carbon dioxide by the little understood process of photo-synthesis (*i.e.* by the influence of light). Such carbohydrates are starch and fructose. The most important carbohydrates which are found in the animal body are glycogen and glucose. Glucose is derived from the breakdown of all the various carbohydrates in the food and from it are built up by the animal body glycogen and lactose. Carbohydrates are so-called because their molecule contains two atoms of hydrogen to one of oxygen, like water. As we have already noted, their carbon and hydrogen are the chief fuels of the body.

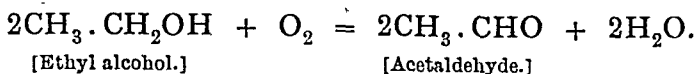
Chemically the sugars are related to the alcohols.

A primary alcohol is one in which the hydroxyl group (OH) and *two* hydrogen atoms are attached to the same carbon atom; it there-

fore contains the group $-\text{CH}_2\text{OH}$. Thus the formula for common alcohol (ethyl alcohol) is $\text{CH}_3 \cdot \text{CH}_2\text{OH}$.

The next alcohol of the same series (primary propyl alcohol) has the formula, $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2\text{OH}$.

If a primary alcohol is oxidised, the first oxidation product is called an *aldehyde*; thus ethyl alcohol yields acetaldehyde:—



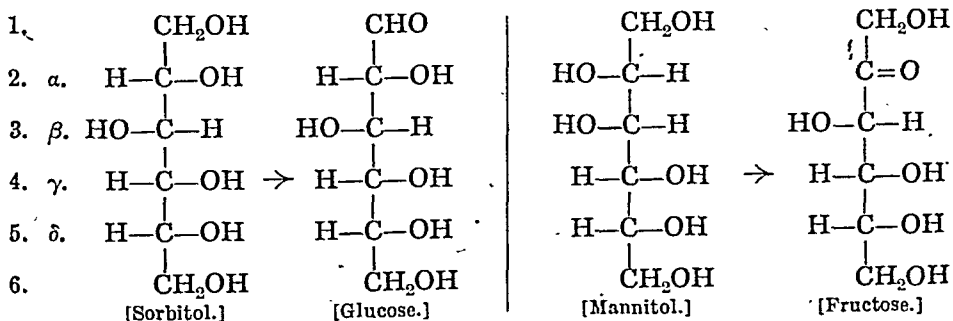
The typical group $-\text{CHO}$ of the aldehyde is not stable, but is easily oxidisable to form the group $-\text{COOH}$ (carboxyl), and the compound so formed is an acid; in this way acetaldehyde forms acetic acid.

The majority of the simple sugars are oxidation products of more complex alcohols than this. Those with aldehyde groups are called *aldoses*. The readiness with which aldehydes are oxidisable renders them powerful reducing agents and readily recognisable.

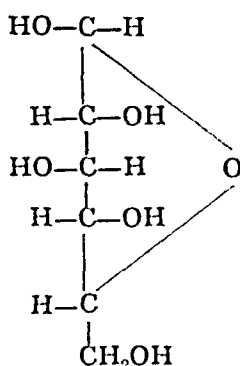
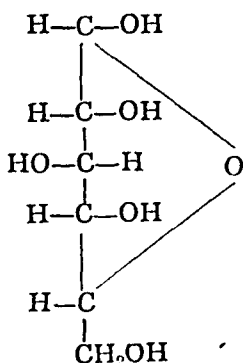
Use is made of this in the Fehling's and Benedict's tests for sugar in which a cupric salt is reduced to cuprous oxide.

A secondary alcohol is one in which the hydroxyl group and only *one* hydrogen atom are attached to the same carbon atom; thus secondary propyl alcohol has the formula $\text{CH}_3 \cdot \text{CHOH} \cdot \text{CH}_3$. Its typical group is therefore $=\text{CHOH}$. When this is oxidised, thus:—
 $2\text{CH}_3 \cdot \text{CHOH} \cdot \text{CH}_3 + \text{O}_2 = 2\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_3 + 2\text{H}_2\text{O}$. The first oxidation product is acetone, which gives the name *ketone* to all substances similarly produced. The only important *ketose*, *i.e.* a sugar which is an oxidation product of a secondary alcohol, is fructose. It is to be noted that all keto-bodies contain the typical keto-group: CO . They are, as will be seen in relation to metabolism, very important in the oxidation of amino acids and fatty acids.

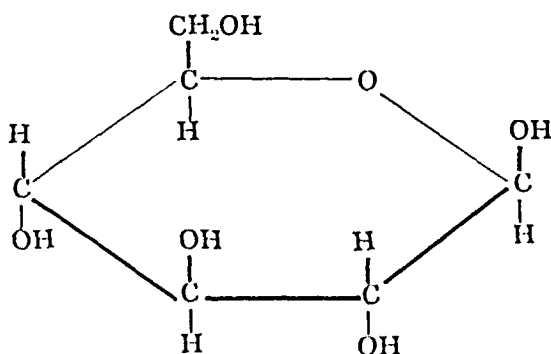
The alcohols of which we have already spoken, *e.g.* ethyl alcohol (see above) are called *monohydric*, because they contain only one OH group. The sugars of physiological interest are derived from three hexahydric alcohols which contain six OH groups as indicated below. These alcohols, sorbitol, mannitol, and dulcitol are isomerides.



The reactions of glucose indicate that it has a ring structure and that two forms exist, α and β .



From a study of the reactions of ring compounds it is indicated that the formula should be more properly written thus:—



It is possible to construct a model showing the exact position of the atoms in their different planes. These facts probably all have a bearing on the method by which glucose is broken down in the animal.

Such sugars are known as **monosaccharides**.

The next important group of sugars is the **disaccharides**, formed by the condensation of two monosaccharides, with the loss of one molecule of water:— $\text{C}_6\text{H}_{12}\text{O}_6 + \text{C}_6\text{H}_{12}\text{O}_6 = \text{C}_{12}\text{H}_{22}\text{O}_{11} + \text{H}_2\text{O}$. If more than two monosaccharide molecules undergo a corresponding condensation, we get **polysaccharides**:— $n\text{C}_6\text{H}_{12}\text{O}_6 = (\text{C}_6\text{H}_{10}\text{O}_5)_n + n\text{H}_2\text{O}$. If boiled with dilute acid the condensation is reversed and the compound sugars split up into their constituent monosaccharides.

Sugars are known to chemists, in which the number of carbon atoms is 3, 4, 5, etc. Certain nucleic acids contain a pentose (5 carbon atoms).

The chief members of the three groups may be arranged in tabular form as follows:—

1. Monosaccharides, $C_6H_{12}O_6$.	2. Disaccharides, $C_{12}H_{22}O_{11}$.	3. Polysaccharides, $(C_6H_{10}O_5)_n$
+ Glucose. R. - Fructose. R. + Galactose. R.	+ Sucrose. + Lactose. R. + Maltose. R.	+ Starch. + Glycogen. + Dextrin. - Inulin. Cellulose.

The R's indicate the **reducing sugars**, that is, those whose free CHO or CO groups reduce copper solutions.

The + and - signs in the above list indicate that the substances to which they are prefixed are dextro- and lævo-rotatory respectively as regards polarised light. The formulæ given in the table are merely empirical; the quantity n in the starch group is large.

It is usual to classify the various sugars according to the number of carbon atoms they contain. Those which we have just described are hexoses (or 6-carbon sugars). **Pentoses** (5-carbon sugars) occur more rarely in the body, but **trioses** (3-carbon sugars) are more common as some are breakdown products of the oxidation of glycogen. As they are closely related to glycerol they are discussed later in relation to fats.

Glucuronic acid is a hexuronic acid derived from glucose by the oxidation of the primary alcohol group to COOH. It is easily formed in the body apparently when there is a demand for the excretion of many poisonous substances used in therapeutics, *e.g.* salicylates, morphine, etc. The importance of the glucuronates is that as they reduce Fehling's solution they may be mistaken for glucose in the urine.

The Polarimeter.

This instrument is one by means of which the action of various substances on the plane of polarised light can be observed and measured. Most of the carbohydrates are dextro-rotatory. The proteins are lævo-rotatory.

There are many varieties of the instrument; these can be properly studied only in the laboratory, but briefly the principles on which they are constructed may be given.

Suppose one is shooting arrows at a fence made up of narrow vertical palings; suppose also that the arrows are flat like the laths of a venetian blind. If the arrows are shot vertically they will pass easily through the gaps between the palings, but if they are shot horizontally they will be unable to pass through at all. This rough illustration will help us in understanding what is meant by polarised light. Ordinary light is produced by the undulations of the ether occurring in all directions at right angles to the path of propagation of the wave. Polarised light is produced by undulations in one plane only.

In a polarimeter, there is at one end of the instrument a Nicol's prism, which is made of Iceland spar. This polarises the light which passes through it; it is called the polariser. At the other end of the instrument is another called the

analyser. Between the two is a tube which can be filled with fluid. If the analyser is parallel to the polariser the light will pass through to the eye of the observer. But if the analyser is at right angles to the polariser it is like the flat arrows hitting horizontally the vertical palings of the fence, and there is darkness. At intermediate angles there will be intermediate degrees of illumination.

If the analyser and polariser are parallel and the intermediate tube filled with water, the light will pass as usual, because water has no action on the plane of polarised light. But if the water contains sugar or some "optically active" substance in solution, the plane is twisted in one direction or the other according as the substance is dextro- or lævo-rotatory and illumination is reduced. The amount of rotation is measured by the number of degrees through which the analyser has to be turned in order to obtain the full illumination. This will vary with the length of the tube and the strength of the solution.

Glucose (Dextrose, or Grape Sugar).—This substance has been described as "the current carbohydrate coin of the body." It is found in many fruits, honey, and in minute quantities in all tissues and fluids of the body. It is the form of sugar which is found normally in the blood and in the disease *diabetes mellitus* in the urine. Glucose exists in nature as such in onions, sweet corn, and unripe potatoes in the process of building up starch. It is present also in the juices of fruits and plants and is usually associated with fructose.

Glucose is soluble in hot and cold water and in alcohol. It is crystalline, but not so sweet as cane-sugar. When heated with strong alkalis certain complex substances are formed which have a yellow or brown colour. This constitutes *Moore's test* for sugar. In alkaline solutions glucose reduces salts of silver, bismuth, mercury, and copper.

This latter reduction which, as we have said, is due to the CHO group, is made use of extensively in testing for sugars.

On warming a solution of glucose with an alkaline solution of picric acid, a dark red opaque solution due to the reduction of picric acid to picramic acid is produced.

Another important property of glucose is that under the influence of yeasts it is converted into ethyl alcohol and carbonic acid.

Glucose may be estimated by the fermentation test, by the polarimeter, and by the use of Fehling's or similar solutions. (See *Urine*.)

Fructose (or Lævulose).—When cane-sugar is treated with dilute mineral acids it undergoes a process known as hydrolysis—*i.e.* it takes up water and is converted into equal parts of glucose and fructose. The previously dextro-rotatory solution of cane-sugar then becomes lævo-rotatory, the lævo-rotatory power of the fructose being greater than the dextro-rotatory power of the glucose formed. Hence the term *inversion* applied to this hydrolysis. The same hydrolytic change is produced by certain enzymes, such as the invertase of the intestinal juice and of yeast. Pure fructose can be crystallised with difficulty. It gives many of the reactions of

glucose, but may be identified by its lævo-rotation, and certain chemical tests.

Galactose is formed by the action of dilute mineral acids or of hydrolytic enzymes on lactose. It resembles glucose in its action on polarised light, in reducing cupric salts, and in being directly fermentable with some yeasts. When oxidised by means of nitric acid it yields an acid, *mucic acid*, which is only slightly soluble in water. Glucose, when treated in this way, yields an isomeric acid—*i.e.* an acid with the same empirical formula, *saccharic acid*, which is very soluble in water.

Cane-Sugar (or Sucrose) is generally distributed in the vegetable kingdom, but especially in the juices of the sugar cane, beetroot, mallow, and sugar maple. It is a substance of great importance as a food. It undergoes inversion in the alimentary

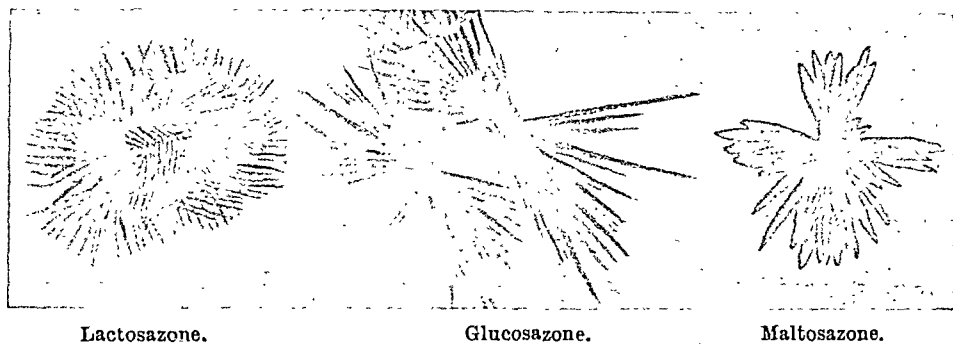


FIG. 123.

canal. It is crystalline, and dextro-rotatory. With Trommer's test it gives a blue solution, but it does not reduce copper solutions because in the union of its two constituent sugars, their aldehydic and ketonic groups are no longer functionally active. After hydrolysis the products are strongly reducing. Hydrolysis may be accomplished by boiling with dilute mineral acids, or by means of enzymes such as those occurring in the intestinal juice. It then takes up water, and is split into equimolecular proportions of glucose and fructose ($C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6$). With yeast, cane-sugar is first inverted by means of a special enzyme *invertase* secreted by the yeast cells, and then there is an alcoholic fermentation of the monosaccharides so formed, which is accomplished by another enzyme called *zymase*.

Lactose (or Milk Sugar) occurs in milk. It is occasionally found in the urine of women in the early days of lactation, or after weaning. It is crystallisable, dextro-rotatory, much less soluble in water than other sugars, and has only a slightly sweet taste. It gives reduction tests, but when the reducing power is tested

quantitatively by Fehling's solution it is found to be a less powerful reducing agent than glucose, in the proportion of 7 to 10. When hydrolysed by agencies similar to those mentioned in connection with sucrose, it takes up water and yields glucose and galactose. With yeast it is first hydrolysed, and then alcohol is formed; the change, however, occurs much more slowly than with other agents.

The lactic acid fermentation which occurs when milk turns sour is brought about by certain micro-organisms, which are somewhat similar to yeast cells. Bacteria in the intestine bring about the same result.

Maltose (or Malt Sugar) is so-called as it is the sugar produced by the action of malt diastase in the first stage of brewing. It is present in germinating cereals, and therefore in malt. It is the chief end-product of the action of malt diastase on starch, and is also formed as an intermediate product in the action of dilute acid on the same substance. It is the only sugar formed from starch by the diastatic enzymes contained in the saliva and pancreatic juice. It can be obtained in the form of acicular crystals, and is strongly dextro-rotatory. It gives reduction tests; but its reducing power, as measured by Fehling's solution, is one-third less than that of glucose. By prolonged boiling with water, or, more readily, by boiling with a dilute mineral acid, or by means of a hydrolytic enzyme such as occurs in the intestinal juice, it is converted into glucose.

Reaction with Phenylhydrazine.—The three important reducing sugars with which we have to deal in physiology are glucose, lactose, and maltose. They may be distinguished by their relative reducing powers on Fehling's solution, or by the characters of their osazones. The osazone is formed in each case by adding phenylhydrazine hydrochloride and sodium acetate, and boiling the mixture for about half an hour. In each case the osazone is deposited in the form of bright canary-coloured, needle-like crystals, usually in bunches, which differ in their crystalline form, melting-point, and solubilities (fig. 123). The osazone of glucose is insoluble in hot water, but those of maltose and lactose are only deposited on cooling. Cane-sugar does not yield an osazone.

Polysaccharides.—The work of Irvine of St Andrews has shown that the constitution of the polysaccharides is simpler than was formerly considered. Without entering into chemical details he has demonstrated that starch, glycogen, and cellulose have as their *essential units* a condensation product of one molecule of glucose and one molecule of a disaccharide, *e.g.* maltose or cellobiose. The manner of linking is different in the three carbohydrates. Inulin (the polysaccharide of artichokes and dahlia tubers) is formed by condensation of fructose molecules.

Starch is widely diffused through the vegetable kingdom. By far its most important sources are ripe cereals and potatoes, but it is present in many unripe fruits before it is converted into sugars and in many roots and tubers. It occurs in nature in the form of microscopic grains, varying in size and appearance, according to their source. Each consists of more or less concentric envelopes of starch proper or granulose alternating with layers of cellulose. Cellulose has no nutritive value in man, but starch is an important food.

Starch forms an opalescent solution in boiling water, which if concentrated gelatinises on cooling. Its most characteristic reaction is the blue colour it gives with iodine. On heating starch with mineral acids, glucose is formed. By the action of diastatic enzymes, maltose is the chief end-product. In both cases dextrans are also formed intermediately.

Dextrans are the intermediate products in the hydrolysis of starch or glycogen to sugar, and two chief varieties are distinguished: *erythro-dextrin*, which gives a reddish-brown colour with iodine; and *achroo-dextrin*, which does not.

The dextrans are readily soluble in water, but insoluble in alcohol and ether. They are amorphous, dextro-rotatory, and do not ferment directly with yeast. By hydrolysing agencies they are converted into glucose.

Glycogen (or Animal Starch) is found in liver and muscle. It is also abundant in white blood corpuscles and embryonic tissues. The auriculo-ventricular bundle has relatively more than the rest of the heart.

Glycogen is rapidly broken down to glucose by glycogenase when a tissue such as liver is removed from the body. This is prevented by throwing it at once into boiling water to destroy the enzyme. When the tissue is ground up and extracted the extract after separation of the proteins is opalescent because of the glycogen it contains.

Glycogen is the form in which carbohydrate is stored in the body. That in the liver is available for general use in the body, but that in the muscle is not so readily utilisable but combines with phosphoric acid and is converted in various stages to lactic acid and eventually to carbon dioxide and water. (See Utilisation of Carbohydrates.)

Glycogen is a white, tasteless non-crystalline powder, soluble in water, but it forms, like starch, an opalescent solution. It is insoluble in alcohol and ether. It is dextro-rotatory. With copper solutions it gives no reduction on boiling. With iodine it gives a reddish or port-wine colour, very similar to that given by erythro-dextrin.

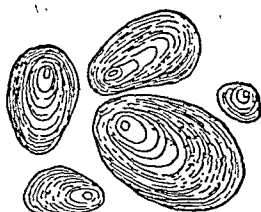


FIG. 124.—Grains of potato starch.

Dextrin may be distinguished from glycogen by (1) the fact that it gives a clear, not an opalescent, solution with water; and (2) it is not precipitated by basic lead acetate as is glycogen. It is, however, precipitated by basic lead acetate and ammonia. (3) Glycogen is precipitated by 55 per cent. of alcohol; the dextrans require 85 per cent. or more. (4) Glycogen is precipitated by saturation with ammonium sulphate; erythro-dextrin is only partially precipitable by this means.

Cellulose.—This is the material which with other carbohydrates (lignin, etc.) makes up the cell-walls and woody fibres of plants. By treatment with strong mineral acids it is, like starch, converted into glucose, but with much greater difficulty. The various digestive enzymes have little or no action on cellulose; hence the necessity of boiling starch before it is taken as food. Boiling bursts the cellulose envelopes of the starch grains, and so allows the digestive juices to get at the starch proper. Cellulose is found in a few animals, as in the outer investment of the Tunicates. Its chief importance in relation to man is that it constitutes the indigestible bulk of the food which is important in regard to the movements of the alimentary canal.

Inositol or Inosite occurs in muscle, also in smaller quantities in other animal organs (liver, kidney, etc.), and in plants it is a fairly constant constituent of roots and leaves, especially growing leaves. It has the same empirical formula as the simple sugars ($C_6H_{12}O_6$), but it has none of the other properties of these substances.

THE FATS OR SIMPLE LIPIDES.

Fat is found in small quantities in many animal tissues. It is found in large quantities in three situations, viz., marrow, adipose tissue, and mammary gland, especially during lactation. The contents of the fat cells of adipose tissue are fluid during life, the normal temperature of the body ($37^{\circ}C.$, or $99^{\circ}F.$) being considerably above the melting-point ($25^{\circ}C.$) of the mixture of the fats found there. The plant world has, however, become an important source of fats for man from which margarines are partly made. Thus we have oil from the palm, soya bean, cotton seed, various nuts and from the olive. The latter is largely used in cooking in Italy. As we shall see later, the fats, in addition to being used as fuel, are an important vehicle for vitamins A, D, and B₆.

The chief fats are three in number, and are called *palmitin*, *stearin* and *olein*. They differ from one another in chemical composition and in certain physical characters, such as melting-point and solubility. Mixed triglycerides also occur. Olein melts at $-5^{\circ}C.$, palmitin at $45^{\circ}C.$, and stearin at $53-65^{\circ}C.$ It is thus olein which holds the other two dissolved at body temperature. Fats are all soluble in hot alcohol, ether, and chloroform, but insoluble in water.

Chemical Constitution of the Fats.—Fats are esters of fatty acids with glycerol. The acids concerned form a series of acids derived from monohydric alcohols by oxidation. Thus, to take ordinary ethyl alcohol, $C_2H_5.OH$, the first stage in oxidation is the formation of acetaldehyde, $CH_3.CHO$; on further oxidation acetic acid, $CH_3.COOH$, is produced.

A similar acid can be obtained from all the other alcohols, thus:

From methyl alcohol	$CH_3.OH$,	formic acid	$H.COOH$ is obtained.
.. ethyl ..	$C_2H_5.OH$,	acetic ..	$CH_3.COOH$..
.. propyl ..	$C_3H_7.OH$,	propionic ..	$C_2H_5.COOH$..
.. butyl ..	$C_4H_9.OH$,	butyric ..	$C_3H_7.COOH$..
.. amyl ..	$C_5H_{11}.OH$,	valeric ..	$C_4H_9.COOH$..
.. hexyl ..	$C_6H_{13}.OH$,	caproic ..	$C_5H_{11}.COOH$..

The sixteenth acid of this series, **palmitic acid**, has the formula $C_{15}H_{31}.COOH$; the eighteenth has the formula $C_{17}H_{35}.COOH$, and is **stearic acid**. Note the small amount of oxygen relative to the hydrogen and compare the carbohydrates.

Oleic acid, however, is not a member of this series, but belongs to a somewhat similar series known as the *acrylic series*. It is the eighteenth member of the series, and its formula is $C_{17}H_{33}.COOH$.

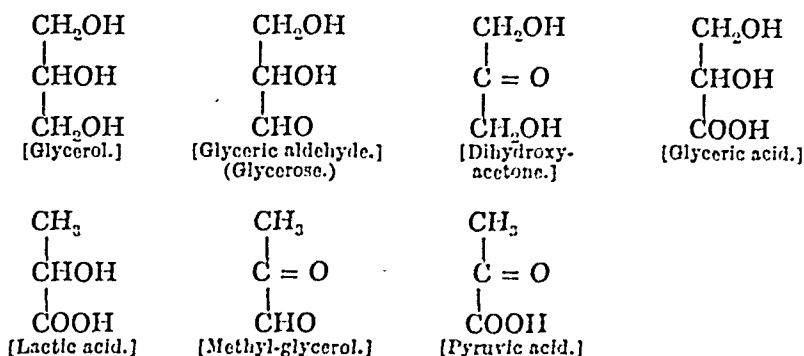
The first member of the group of alcohols from which this acrylic series of acids is obtained is called *allyl alcohol* ($CH_2:CH.CH_2OH$); the corresponding aldehyde *acrolein* ($CH_2:CH.CHO$); the formula for the acid (acrylic acid) is $CH_2:CH.COOH$. It will be noticed that two of the carbon atoms are united by a double bond, and these substances are therefore unsaturated; they are unstable and are prone to undergo, by uniting with another element, a conversion into substances in which the carbon atoms are united by only one bond. This accounts for their reducing action, and it is owing to this that the colour reactions with osmic acid and Sudan III (red coloration) are due. Fat which contains any member of the acrylic series, such as oleic acid, blackens osmic acid (OsO_4), by reducing it to a lower (black) oxide, probably in hydrated form. The fats palmitin and stearin containing no double bond do not give these reactions.

Glycerol or Glycerine is a trihydric alcohol, $C_3H_5(OH)_3$ —i.e. three hydroxyl groups united to a radical glyceryl ($C_3H_5\equiv$). The hydrogen in the hydroxyl groups is replaceable by organic radicals. As an example, the radical of acetic acid the *acetyl* group ($CH_3.CO-$) may be taken. The following formulæ represent the derivatives that can be obtained by replacing one, two, or all three hydroxyl hydrogen atoms in this way:

$CH_2.OH$	$CH_2.OH$	$CH_2.OH$	$CH_2.O.OC.CH_3$
$CH.OH$	$CH.OH$	$CH.O.OC.CH_3$	$CH.O.OC.CH_3$
$CH_2.OH$	$CH_2.O.OC.CH_3$	$CH_2.O.OC.CH_3$	$CH_2.O.OC.CH_3$
[Glycerol.]	[Monoacetin.]	[Diacetin.]	[Triacetin.]

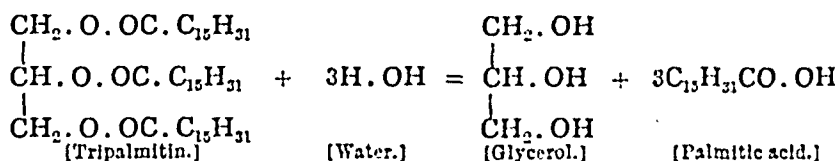
Triacetin is a type of a neutral fat; stearin, palmitin, and olein ought more properly to be called *tristearin*, *tripalmitin*, and *triolein* respectively.

When oxidised, glycerol gives rise to two important trioses (3-carbon sugars), glyceric aldehyde (an aldose) and dihydroxyacetone (a ketose). They are also related to other important substances as indicated by their formulæ.

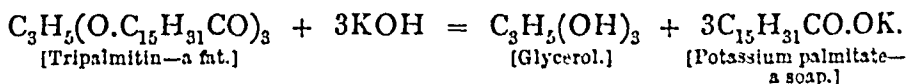


Many of these substances are also breakdown products of glycogen.

Decomposition Products of the Fats.—Under the influence of superheated steam, mineral acids, and in the body by means of certain enzymes (for instance, the fat-splitting enzyme lipase of the pancreatic juice), a fat combines with water and splits into glycerol and the fatty acid. The following equation represents what occurs in a fat, taking tripalmitin as an example:—



In the process of **saponification** much the same sort of reaction occurs, the final products being glycerol and a compound of the alkali used with the fatty acid; this is called a *soap*. Suppose, for instance, that potassium hydrate is used, the following reaction occurs:—



The amount of KOH in milligrammes necessary to produce a soap from one gram of fat is known as the *saponification value* of a fat and gives the mean molecular weight of the fatty acids it contains. The higher the saponification value the more fatty acids of low molecular weight the fat contains.

All natural fats contain some fatty acids which are unsaturated, and which, therefore, take up the halogens easily. The number

of milligrammes of iodine taken up by a gram of fat is known as its *iodine value*. This gives an idea of the reactivity of the fats and is of value in recognising an unknown fat. Butter has an iodine value of 25-50, while most vegetable oils have a value of over 100, *e.g.* cotton-seed oil 144-168. Some of the unsaturated fats, *e.g.* olein, can be caused, under suitable conditions, to take up hydrogen which may make them more palatable. This process of hydrogenation is used in the making of margarine.

Fats tend to become rancid if kept in a hot moist atmosphere. A partial hydrolysis occurs leading to the liberation of fatty acids, some of which, like the butyric of butter, may be volatile and smell.

Oxidation of fats also occurs and is well seen in the tough skin which appears on oil paint.

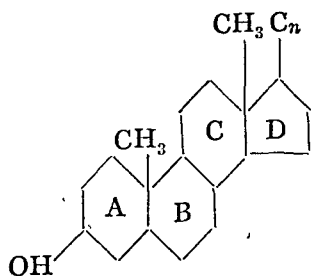
Emulsification.—Another change that fats undergo in the body is very different from saponification. It is a physical, not a chemical change; the fat is broken up into very small globules such as are seen in the natural *emulsion*—milk.

THE STEROLS.

The sterols with other substances which, like the fats, are soluble in ether and alcohol, used to be included under the general term "lipoid," but this term has now been given up.

They are found mixed with fat in the ether-alcohol extract of tissues and organs, but are non-saponifiable. They are specially abundant in nervous tissues; they can be separated by what is called selective extraction.

The *sterols* are alcohols of a high molecular weight with a complicated ring structure. Thus:



The rings are composed of C, CH, or CH₃ groups, but C_n is very variable.

Amongst the sterols are now known to be not only cholesterol but ergosterol, the bile acids, vitamin D, and the sex hormones. Many carcinogens (*i.e.* substances which applied to the skin produce a cancerous overgrowth of the epithelium) are also sterols.

Cholesterol is found in small quantities in all forms of protoplasm. It is a specially abundant constituent of nervous tissues. It is found in small quantities in the bile, but it may occur there in excess and form the concretions known as gall-stones. It occurs in egg yolk, liver, suprarenal, kidney, and in animal fats generally.

It is a monohydric unsaturated alcohol with the empirical formula $C_{27}H_{45}.OH$. The alcohol belongs to the terpene series, which are found as excretory products of plant life.

Cholesterol is now believed to be not merely a waste product of metabolism, but to exert an important protective influence on the body cells against the

entrance of certain poisons. One of the poisons contained in cobra venom dissolves red blood-corpuscles; the presence of cholesterol in the envelope of the blood-corpuscles to some extent hinders this action, and it has been stated that the administration of cholesterol increases the resistance of the animal provided the unsaturated linkage is intact.*

An ester of cholesterol is lanolin or wool-fat. A similar substance is found in the fatty secretion (sebum) of human skin.

From alcohol or ether containing water, cholesterol crystallises in the form of rhombic plates, which contain one molecule of water of crystallisation: these are easily recognised under the microscope (fig. 125) and their edges turn red with sulphuric acid.

Ergosterol.—This sterol derives its name from its having first been derived from ergot of rye. It is usually prepared from yeast. It has the same ring structure as cholesterol, but contains three double bonds and a methyl group. It has the extremely important property of being converted into vitamin D by ultra-violet light. It was first thought that the light acted upon the cholesterol of the plants but the irradiation of pure cholesterol did not give the vitamin. Many years before, however, it had been found by Rosenheim when studying the chemistry of nerve tissues with Halliburton that ergosterol was a common impurity in cholesterol and this was shown to be activated. This transformation may be brought about in food-stuffs whose vitamin has been destroyed by heat, and it is believed that the ergosterol of the skin is normally activated in this way and passes into the circulation, where it plays an important part in the

* The blood cholesterol is increased by giving uracil to counteract overaction of the thyroid.

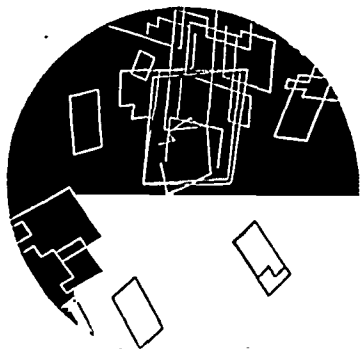


FIG. 125.—Cholesterol crystals.

absorption of calcium from the intestine and its deposition in the bones (see vitamin D).

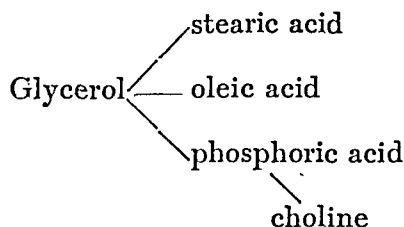
Calciferol, or pure vitamin D, has now been synthesised and shown to be an isomer of ergosterol.

THE LIPINS OR COMPOUND LIPIDES.

These are substances having the general composition and properties of fat, but containing in addition phosphoric acid and choline or occasionally amino-ethyl alcohol. Much the most important of these are the **Lecithins**, which are now considered to be possibly a stage in the metabolism of fat. They are found in all animal and vegetable cells, are intimately associated with life processes, and probably have an important function in the membranes of cells. The endothelium lining blood-vessels and the envelopes of blood corpuscles are especially rich in lecithins. Liver and blood contain about 2 per cent. but egg yolk about 10 per cent. A lecithin has the appearance of a soft fat, soluble in the usual fat solvents but is precipitated by acetone. They make slimy colloidal emulsions in water in which they can be spread in a monomolecular film.

The fatty acid radicals are united to glycerol as in an ordinary fat, the place of the third fatty acid being taken by the radical of the polybasic phosphoric acid, which in its turn is united in an ester-like manner to the choline. Because they contain phosphorus they have also been called phosphatides. Lecithins from different sources yield, when hydrolysed, varying proportions of fatty acids.

In general structure a lecithin looks like a simple fat plus choline. Thus egg-yolk lecithin is:—



The enzyme lipase liberates the aliphatic acids and another, phosphatase, the phosphoric acid. In some (*e.g.* liver) lecithins, palmitic acid replaces those given. **Choline** has considerable physiological activity, but still more has its derivative acetyl-choline, which is liberated at nerve-endings. It has already been referred to in relation to the humoral transmission of nerve impulses, and its detailed action is given in a separate section (see Acetyl-choline).

Other *phosphatides* are kephalin and sphingomyelin and the galactoside, protagon, which are abundant in nerve tissues and which differ slightly from lecithin. Closely associated are the cerebroside of the myelin sheaths of nerves. Kephalin is thought to be important in blood-clotting.

Osmic Acid Reaction.—In virtue of their unsaturated fatty acid radicals most fats are blackened readily by this reagent, but the galactosides and cholesterol are not. The reaction to this reagent of healthy and degenerated nerve-fibres has already been described.

THE PROTEINS.

The **proteins** are the most important substances which occur in animal and vegetable organisms, and *protein metabolism* is, as already noted, the most characteristic sign of life. They are highly complex compounds of carbon, hydrogen, oxygen, nitrogen, and sulphur,* with at times phosphorus, occurring in a viscous condition or in pseudo-solution in nearly all parts of the body.

The proteins in the food form the source of the proteins in the body tissues, but the latter are usually different in composition from the former. The food proteins in the process of digestion are broken down into simpler substances, the amino-acids, and it is from these that the body cells reconstruct the proteins peculiar to themselves.

CLASSIFICATION OF PROTEINS.

The knowledge of the chemistry of the proteins, which is slowly progressing, will, no doubt, in time enable us to give a classification of these substances on a strictly chemical basis. The following classification must be regarded as a provisional one, which, while it retains the old familiar names as far as possible, yet attempts also to incorporate some of the new ideas.

The classes of animal proteins, then, beginning with the simplest, are as follows:—

- | | |
|---------------------|-------------------------|
| 1. Protamines. | 6. Phospho-proteins. |
| 2. Histones. | 7. Conjugated proteins. |
| 3. Albumins. | i. Chromo-proteins. |
| 4. Globulins. | ii. Gluco-proteins. |
| 5. Sclero-proteins. | iii. Nucleo-proteins. |

There are in addition two important groups of simple proteins in plants, Gliadins and Glutenins.

1. The Protamines.

These substances are obtainable from the heads of the spermatozoa of certain fishes, where they occur in combination with nuclein. Kossel's view that they are the simplest proteins in nature has met with general acceptance, and they give such typical protein reactions as the biuret (Rose's or Piotrowski's) reaction. On hydrolytic decomposition they first yield substances of smaller molecular weight

* The simplest proteins, the *protamines*, are, however, free from sulphur.

analogous to the peptones which are called *protones*, and then they split up into amino-acids. The number of resulting amino-acids is small as compared with other proteins, hence the hypothesis that they are simple proteins is confirmed. Notable among their decomposition products are the diamino-acids or hexone bases, especially arginine. The protamines differ in their composition according to their source, and yield these products in different proportions. Protamines do not contain sulphur.

2. The Histones.

These are substances which have been separated from blood-corpuscles; *globin*, the protein constituent of hæmoglobin, is a well-marked instance. They yield a larger number of amino-compounds than do the protamines, but diamino-acids are still relatively abundant. They are coagulable by heat, soluble in dilute acids, and precipitable from such solutions by ammonia. The precipitability by ammonia is a property possessed by no other protein group.

3. The Albumins.

These are typical proteins, and yield the majority of the cleavage products enumerated later.

They enter into colloidal solution in water, in dilute saline solutions, and in saturated solutions of sodium chloride and magnesium sulphate. They are, however, precipitated by saturating their solutions with ammonium sulphate. Their solutions are coagulated by heat, usually at 70-73° C. Serum albumin, egg albumin, and lact-albumin are instances.

4. The Globulins.

The globulins give the same general tests as the albumins; they are coagulated by heat, but differ from the albumins mainly in their solubilities.

Globulins are more readily salted out than albumins; they may therefore be precipitated; and thus separated from the albumins by saturation with such salts as sodium chloride, or better magnesium sulphate, or by half saturation with ammonium sulphate.

The typical globulins are also insoluble in water, and so may be precipitated by removing the salt which keeps them in solution. This may be accomplished by dialysis. Their temperature of heat-coagulation varies considerably. The following are the commoner globulins:—fibrinogen and serum globulin in blood, egg globulin in white of egg, paramyosinogen in muscle, and crystallin in the crystalline lens. We must also include under the same heading

certain proteins which are the result of coagulation of globulins, such as fibrin (see Blood) and myosin (see Muscle).

The most striking distinction between globulins and albumins is that the former on hydrolysis yield glycine, whereas the albumins have only a trace.

5. The Sclero-proteins.

These substances form a heterogeneous group of substances which were formerly termed *albuminoids*. The prefix sclero- indicates the skeletal origin and often insoluble nature of the members of the group. The principal proteins of this class are:—

Collagen, the substance of which the white fibres of connective tissue are composed. Some observers regard it as the anhydride of gelatin. In bone it is often called *ossein*.

Gelatin.—This substance is produced by boiling collagen with water. It possesses the peculiar property of setting into a jelly when a solution made with hot water cools. Gelatin differs from a protein in not having the amino-acids, tryptophane, tyrosine, and cystine.

Elastin.—This is the substance of which the yellow or elastic fibres of connective tissue are composed. It is a very insoluble material. The sarcolemma of muscle-fibres and certain basement membranes are very similar.

Keratin, or horny material, is the substance found in the surface layers of the epidermis, in hairs, nails, hoofs, and horns. It is very insoluble, and chiefly differs from most other proteins in its high percentage of sulphur. A similar substance, called *neurokeratin*, is found in neuroglia and nerve-fibres. In this connection it is interesting to note that the epidermis and the nervous system are both formed from the same layer of the embryo—the ectoderm.

6. The Phospho-proteins.

Vitellin (from egg-yolk), caseinogen, the principal protein of milk, and casein, the result of the action of the rennet-enzyme on caseinogen (see Milk), are the chief members of this group. Among their decomposition products is a considerable quantity of phosphoric acid. They have been frequently confused with the nucleo-proteins, but they do not yield the products (purine and other bases) which are characteristic of nucleo-compounds. The phosphorus is contained within the protein molecule, and not in another molecular group united to the protein, as is the case in the nucleo-proteins. The phospho-proteins are specially valuable for the growth of young and embryonic animals. Many other proteins, such as serum-globulin, contain traces of phosphorus.

7. The Conjugated Proteins.

These are compounds in which the protein molecule is united to other organic materials, which are as a rule also of complex nature. This second constituent of the compound is usually termed a *prosthetic group*. They may be divided into the following sub-classes:—

i. Chromo-proteins.—These are compounds of protein with a pigment, which usually contains iron. They are exemplified by hæmoglobin and its allies, which will be fully considered under Blood.

ii. Gluco-proteins.—These are compounds of protein with a carbohydrate group. This class includes the mucins and the mucoids.

The *mucins* are widely distributed and may occur in epithelial cells, or be secreted by goblet cells of glands or on epithelial surfaces. The *mucins* obtained from different sources are alike in being viscid and tenacious, soluble in dilute alkalis such as lime-water, and precipitable from solution by acetic acid.

The *mucoids* differ from the mucins in minor details. The term is applied to the mucin-like substances which form the chief constituent of the ground substance of connective tissues (tendo-mucoid, chondro-mucoid, etc.). Another (ovo-mucoid) is found in white of egg, and others (pseudo-mucin and para-mucin) are occasionally found in dropsical effusions, and in the fluid of ovarian cysts.

iii. Nucleo-proteins.—These are compounds of protein with a complex organic acid called nucleic acid, which contains phosphorus. They are found in both the nuclei and cytoplasm of cells. In physical character they often simulate mucin.

Nuclein is the name given to the chief constituent of cell-nuclei. It is identical with the chromatin of histologists.

On decomposition it yields an organic acid called nucleic acid, together with a variable but usually small amount of protein. It contains a high percentage (10-11) of phosphorus.

The nuclein obtained from the nuclei or heads of the spermatozoa consists of nucleic acid without any protein admixture, but there are differences in different animals in the chemical composition of their spermatozoa.

The *nucleo-proteins of cell protoplasm* are compounds of nucleic acid with a much larger quantity of protein, so that they usually contain only 1 per cent. or less of phosphorus. Some also contain iron, and the normal supply of iron to the body is contained in the nucleo-proteins or *hæmatogens* (Bunge) of plant or animal cells.

Nucleic acid yields, among its decomposition products, phosphoric acid, various bases of the purine and pyrimidine groups, and a carbohydrate radical.

The nucleic acids obtained from various mammalian organs indicate that they fall into two main classes:—

(1) *Nucleic acid proper*.—This yields on decomposition—

- (a) Phosphoric acid. (b) A sugar.
- (c) Two members of the purine group in the same proportion, namely, adenine and guanine.
- (d) Two pyrimidine bases, cytosine and thymine (yeast nucleic acid yields uracil).

The *purine bases* are specially interesting because of their close relationship to uric acid, and we shall have to deal with them again in our description of that substance.

(2) *Guanylic and adenylic acid*.—These acids are found mixed with the nucleic acid proper. They are mononucleolides consisting of guanine, ribose, and phosphoric acid and adenine, ribose, and phosphoric acid respectively. Ribose is a pentose.

The Properties of Proteins.

Solubilities.—The proteins are insoluble* in alcohol and ether. Some are soluble in water (see *Colloidal Solution*); others are insoluble. Many of the latter are soluble in weak saline solutions. Some are insoluble, others soluble in concentrated saline solutions.

Heat Coagulation.—Most native proteins, such as white of egg, are rendered insoluble when their solutions are heated. The temperature of heat coagulation differs in different proteins; thus myosinogen and fibrinogen coagulate at 56° C., serum albumin and serum globulin at about 75° C. The proteins which are coagulated by heat come mainly under two classes: the *albumins* and the *globulins*. These differ in solubility; the albumins are soluble in distilled water, the true globulins require salts to hold them in solution.

Indiffusibility.—The proteins (peptones excepted) belong to the class of substances called *colloids* by Thomas Graham; that is, they pass with difficulty, or not at all, through animal membranes. In the construction of dialysers, vegetable parchment is largely used. Proteins may thus be separated from diffusible (*crystalloid*) substances such as salts, but the process is a tedious one.

This is a particularly important property, since by attracting water they localise fluids in special parts of the body, e.g. the blood-vessels.

Crystallisation.—Hæmoglobin, the red pigment of the blood, is a protein and is crystallisable (for further details, see *The Blood*). Like other proteins it has a large molecule; though crystalline,

* The gliadins are exceptions in being soluble.

it is not crystalloid in Graham's sense of that term. Further, egg albumin and some other proteins have been crystallised by treatment with inorganic salts.

Action on Polarised Light.—Most proteins are lævo-rotatory, the amount of rotation varying with individual proteins. Several of the conjugated proteins, *e.g.* hæmoglobin and nucleo-proteins, are dextro-rotatory, though their protein components are lævo-rotatory (Gamgee).

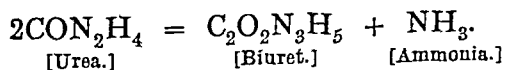
Colour Reactions.—The principal colour reactions by which proteins are recognised are the following:—

(1) The *Xantho-proteic reaction*. If nitric acid is added to a solution of a protein such as white of egg, the result is a white precipitate; this and the surrounding liquid become yellow on heating and are turned orange by ammonia. The preliminary white precipitate is not given by certain proteins such as peptones; but the colours are the same. The colour is due to the formation of nitro-derivatives of the aromatic radical of the protein molecule, *i.e.* tyrosine, tryptophane, and phenylalanine.

(2) *Millon's reaction*. Millon's reagent is a mixture of mercuric and mercurous nitrate with excess of nitric acid. This gives a white precipitate which is turned brick-red on boiling. This reaction depends on the presence of the tyrosine radical and therefore is not given by gelatin.

(3) *Biuret reaction* (*Rose's or Piotrowski's*). A trace of copper sulphate and excess of strong caustic potash give with most proteins a violet solution. Proteoses and peptones, however, give a rose-red colour instead; this same colour is given by the substance called *biuret*. This name does not imply that biuret is present in protein, but is used because both protein and biuret give the reaction. The native proteins give a violet colour, because the red tint of the copper compound with the biuret group is mixed with another copper compound with a blue colour. The test is given by polypeptides but not by dipeptides or amino-acids. It depends, therefore, on the presence of two $\text{NH}\cdot\text{CO}$ groups linked to a carbon on to a nitrogen atom.

Biuret is formed by heating solid urea; ammonia passes off and leaves biuret, thus—



(4) *Adamkiewicz reaction*. When a solution of protein is mixed with a dilute solution of glyoxylic acid, and then excess of commercial sulphuric acid is added, an intense violet colour is obtained. This is due to the tryptophan radical. A similar test is that of *Rosenheim* in which dilute formaldehyde replaces the glyoxylic acid.

Precipitants of Proteins.—Solutions of most proteins are precipitated by:—

Strong acids such as nitric acid; picric acid; acetic acid and potassium ferrocyanide; acetic acid and excess of a neutral salt such as sodium sulphate, when these are boiled with the protein solution; salts of the heavy metals such as copper sulphate, mercuric chloride, lead acetate, silver nitrate, etc.; tannin; alcohol; saturation with certain neutral salts such as ammonium sulphate.

It is necessary that the words *coagulation* and *precipitation* should in connection with proteins be carefully distinguished. The term *coagulation* is used when an insoluble protein (coagulated protein) is formed from a soluble one. This may occur: (1) When a protein is heated—*heat coagulation*; (2) under the influence of an enzyme; for instance, when a curd is formed in milk by rennet or a clot in shed blood by the fibrin ferment—*enzyme coagulation*; (3) under the influence of strong acids.

In *precipitation* the precipitate formed is readily soluble in suitable reagents such as saline solutions, and the protein continues to show its typical reactions. This is called “**salting out**.”* The difference between globulins and albumins in this respect is discussed further on p. 320.

The precipitate produced by alcohol is peculiar in that after a time it becomes a coagulum. Protein freshly precipitated by alcohol is readily soluble in water or saline media; but after it has been allowed to stand some time under alcohol it becomes more and more insoluble. Such a change in the nature of the protein is called **denaturation**. Albumins and globulins are most readily rendered insoluble by this method; proteoses and peptones are never rendered insoluble by the action of alcohol. This fact is of value in the separation of these proteins from others. It is suggested that denaturation is really due to a deformation of the protein molecule from a complicated form (see p. 289) to a straight chain, since the spreading of the protein on a very thin film causes this change. The change in egg-white when it is beaten up with air may be of this nature.

Protein-hydrolysis.

When protein material is subjected to hydrolysis, as it is when heated with mineral acid, or alkalis, or superheated steam, or to the action of such enzymes as **trypsin** in the alimentary canal, it is finally resolved into the numerous amino-acids of which it is built. But before this ultimate stage is reached, it is split into

* Other colloids (starch, glycogen, soaps, etc.) can be similarly “salted out” of solution.

substances of progressively diminishing molecular size, which still retain many of the protein characters. The products may be classified in order of formation as follows:—

1. Meta-proteins.
2. Proteoses.
3. Peptones.
4. Polypeptides.
5. Amino-acids.

The polypeptides are linkages of more than three amino-acids, as already explained. Although most of the polypeptides at present known are products of laboratory synthesis, many have been definitely separated from the digestion products of proteins.

Products of Partial Hydrolysis.

1. **Acid and Alkali Metaprotein.**—These are insoluble in pure water, but are soluble in either acid or alkali, and are precipitated by neutralisation unless certain disturbing influences like sodium phosphate are present. They are precipitated like globulins by saturation with such neutral salts as sodium chloride or magnesium sulphate. They are not coagulated by heat if in solution.

2. **Proteoses.**—The word “proteose” includes the albumoses (from albumin), globuloses (from globulin), vitelloses (from vitellin), etc. Similar substances are also formed from gelatin (gelatinoses) and elastin (elastoses). They are not coagulated by heat; they are precipitated but not coagulated by alcohol: like peptone, they give the pink biuret reaction. They are precipitated by nitric acid, *the precipitate being soluble on heating, and reappearing when the liquid cools*. This last is a distinctive property of proteoses. They are slightly diffusible.

The primary proteoses, which are those formed first, are precipitated by saturation with magnesium sulphate or sodium chloride. Secondary proteose is not; it is, however, precipitated by saturation with ammonium sulphate.

3. **Peptones.**—These are soluble in water, are not coagulated by heat, and are not precipitated by nitric acid, copper sulphate, ammonium sulphate, and a number of other precipitants of proteins. They are precipitated but not coagulated by alcohol. They are also precipitated by tannin, picric acid, potassio-mercuric iodide, phosphomolybdic acid, and phospho-tungstic acid.

They give the biuret reaction (rose-red solution with a trace of copper sulphate and caustic potash or soda).

Peptone is readily diffusible through animal membranes.

The table on p. 284 will give us at a glance the chief characters of

peptones and proteoses in contrast with those of the native proteins, albumins, and globulins.

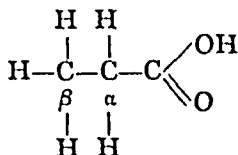
Variety of protein.	Action of heat.	Action of alcohol.	Action of nitric acid.	Action of ammonium sulphate.	Action of copper sulphate and caustic potash.	Diffusibility.
Albumin	Coagulated	Precipitated, then coagulated	Precipitated in the cold; not readily soluble on heating	Precipitated by complete saturation	Violet colour (biuret reaction)	Nil
Globulin	Ditto	Ditto	Ditto	Precipitated by halfsaturation; also precipitated by $MgSO_4$	Ditto	Ditto
Proteoses	Not coagulated	Precipitated, but not coagulated	Precipitated in the cold; readily soluble on heating; the precipitate reappears on cooling*	Precipitated by saturation	Rose-red colour (biuret reaction)	Slight
Peptones	Not coagulated	Precipitated, but not coagulated	Not precipitated	Not precipitated	Rose-red colour (biuret reaction)	Great

* With deutero-albumose this reaction only occurs in the presence of excess of salt.

The Amino-Acids.

What we have already learnt about the fatty acids will help us in understanding what is meant by an **amino-acid**. We shall find it advantageous to distinguish the carbon atoms in the fatty acids.

1. If we take acetic acid, one of the simplest of the fatty acids, its formula is $CH_3 \cdot COOH$. If one of the three hydrogen atoms in the methyl group is replaced by NH_2 , we get a substance which has the formula $CH_2(NH_2)COOH$. The group NH_2 is called the *amino-group*, and the new substance now formed is called *amino-acetic acid*; it is also termed **glycine** or *glycocoll*. In this example there is only one position which the amino-group can occupy. Thus there can only be one amino-acetic acid, but in other cases there are more possibilities, and their carbon atoms are termed α , β , γ , etc. In propionic acid there are two possibilities; it has the formula—



We thus can get either $\text{CH}_2 \cdot \text{NH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$ (β -amino-propionic acid) or $\text{CH}_3 \cdot \text{CH} \cdot \text{NH}_2 \cdot \text{COOH}$ (the α acid); α -amino-propionic acid is called **alanine**. Going higher in the scale, the more numerous become the possibilities, but the α -amino-acids only are found in nature. From β -hydroxy-propionic acid, we get the amino-derivative called **serine**; from valeric acid ($\text{C}_4\text{H}_9 \cdot \text{COOH}$), **valine** ($\text{C}_4\text{H}_8(\text{NH}_2)\text{COOH}$) is obtained; and from caproic acid ($\text{C}_5\text{H}_{11} \cdot \text{COOH}$) we get **leucine** ($\text{C}_5\text{H}_{10}(\text{NH}_2)\text{COOH}$), or more accurately α -amino-isobutyl-acetic acid ($(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2)\text{COOH}$). Its crystalline form is shown on the left-hand side of fig. 126.

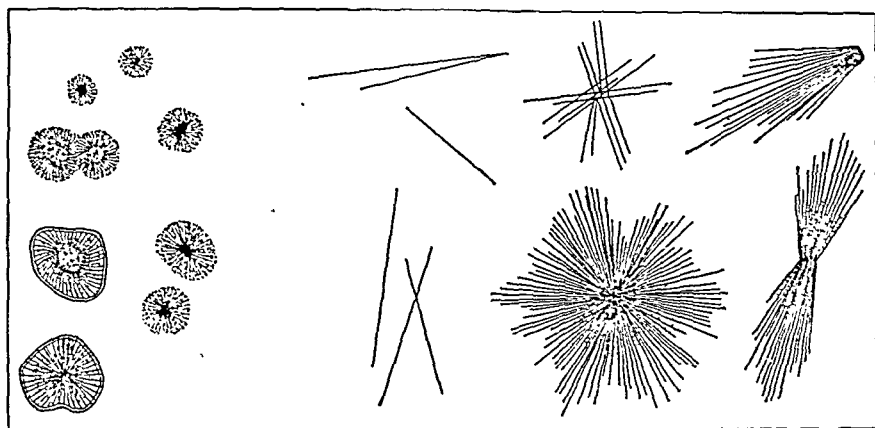


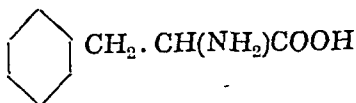
FIG. 126.—Crystals of leucine (left) and tyrosine (right). $\times 216$.

All the five amino-acids (glycine, alanine, serine, valine, and leucine) are found among the final hydrolytic products of most proteins.

2. A second group of amino-acids is obtained from fatty acids, which contain two carboxyl (COOH) groups in their molecules. The most important of the amino-derivatives obtained from these dicarboxylic acids are: amino-succinamic acid (asparagine*); amino-succinic acid (aspartic acid); amino-glutaric acid (glutamic acid).

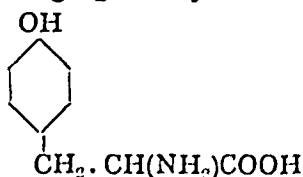
3. The third group of amino-acids is a very important one; the *aromatic amino-acids*; that is, amino-acids containing the benzene ring. The most important are:—

(1) **Phenyl-alanine** is alanine or α -amino-propionic acid in which an atom of hydrogen is replaced by a phenyl group; propionic acid has the formula $\text{C}_2\text{H}_5 \cdot \text{COOH}$; alanine (α -amino-propionic acid) is $\text{C}_2\text{H}_4(\text{NH}_2)\text{COOH}$; phenyl-alanine is $\text{C}_6\text{H}_5 \cdot \text{C}_2\text{H}_3(\text{NH}_2)\text{COOH}$, or graphically written—



* An amide of aspartic acid.

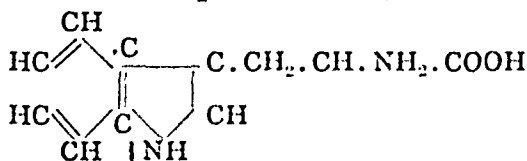
(2) **Tyrosine** is a little more complicated; it is para-hydroxy-phenyl alanine; that is, graphically written—



Tyrosine crystallises in collections of very fine needles (see fig. 126).

Tyrosine is of special importance as it is apparently used by the thyroid gland to form thyroxine and by the adrenal gland to form adrenaline. It also forms tyramine which has an action somewhat like adrenaline on the blood-vessels and is present in ripe cheese and putrefying tissues. When oxidised through the agency of the enzyme tyrosinase (see Raper) it forms the black pigment melanin which is so common in nature.

(3) **Tryptophan** is more complex still—



it is indole amino-propionic acid: that is, amino-propionic acid united to a ringed derivative called indole. Tryptophan is the portion of the protein molecule which is the parent substance of two evil-smelling* products of protein decomposition called indole and skatole or methyl indole. Indole is a combination of the benzene and pyrrol rings. Tryptophan is responsible for the Adamkiewicz reaction and gives a red colour with bromine water.

In this and in all the preceding cases, there is only one replacement of an atom of hydrogen by the amino group (NH_2); hence they may be all classed together as *mono-amino-acids*.

Passing to the next stage in complexity, we come to another group of amino-acids which are called *diamino-acids*; that is, fatty acids in which two hydrogen atoms are replaced by NH_2 groups. Of these we may mention lysine, ornithine, arginine, and histidine.

Lysine is diamino-caproic acid. Caproic acid is $\text{C}_6\text{H}_{11} \cdot \text{COOH}$. Mono-amino-caproic acid or leucine, we have already learnt, is $\text{C}_6\text{H}_{10}(\text{NH}_2)\text{COOH}$. Lysine or diamino-caproic acid is $\text{C}_6\text{H}_9(\text{NH}_2)_2 \cdot \text{COOH}$.

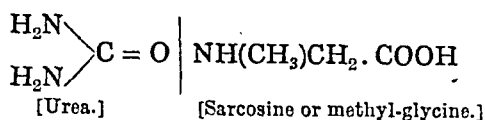
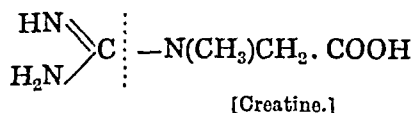
Ornithine is diamino-valeric acid, and the following formulæ will show its relationship to its parent fatty acid—

$\text{C}_4\text{H}_9\text{COOH}$ is valeric acid.

$\text{C}_4\text{H}_7(\text{NH}_2)_2\text{COOH}$ is diamino-valeric acid or ornithine.

* The smell is probably due to skatole, pure indole having a pleasant smell.

Arginine is a somewhat more complex substance, which contains the ornithine radical. It belongs to the same group of substances as **creatine**, which is methyl-guanidine acetic acid, and has the formula—



On boiling it with baryta water, it takes up water and splits at the dotted line into urea and sarcosine, as shown above.

Arginine splits in a similar way, urea being split off on the left, and ornithine instead of sarcosine on the right. Arginine is, therefore, a compound of ornithine with a urea group.

Histidine, though not strictly speaking a diamino-acid, is a diazine derivative (imidazole-amino-propionic acid), and so may be included in the same group. Histidine is of great importance as it readily loses CO_2 on decomposition and gives rise to the toxic substance *histamine*, which is very readily produced in damaged tissues (see special section).

These substances we have spoken of as acids, but they may also play the part of bases, for the introduction of a second amino-group into the fatty acid molecules confers upon them basic properties. The three substances: lysine, $\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2$; arginine, $\text{C}_6\text{H}_{14}\text{N}_4\text{O}_2$; histidine, $\text{C}_6\text{H}_9\text{N}_3\text{O}_2$ are in fact often called the *hexone bases*, because each of them contains 6 atoms of carbon, as the above empirical formulæ show.

Cystine, **cysteine**, and **methionine** are amino-acids in which sulphur is present, and in which the greater part of the sulphur of the protein molecule is contained.

In addition to all these numerous amino-acids there are other cleavage products, of which it will be sufficient to mention **proline**. In the nucleo-proteins the nuclein component yields in addition what are known as **purine** and **pyrimidine** bases. (See further under Nucleic Acid, also under Uric Acid.)

The Constitution of Proteins.

The above list now represents the principal groups of chemical nuclei united together in the protein molecule, and its length makes one realise the complicated nature of that molecule and the difficulties which beset its investigation. We may put the problem another way. In the simple sugars, with six atoms of carbon, there are as many as twenty-four different ways in which the atomic groups may be linked up; the formulæ on p. 263 give only four of these which

represent the structure of glucose, fructose, mannitol, and sorbitol; but the majority of the remainder have also been prepared by chemists. The molecule of albumin has at least 700 carbon atoms, so the possible combinations and permutations must be reckoned by millions.

Much work is being done on the various known proteins, taking them to pieces and identifying and estimating the fragments and improving the methods of estimation. The following table presents the results obtained with some of the cleavage products of a few proteins. The numbers given are percentages.

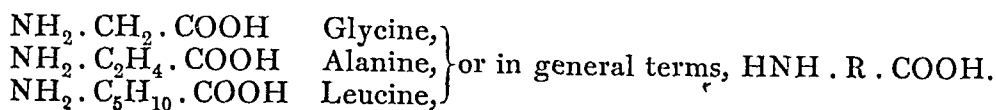
	Serum albumin.	Egg albumin.	Serum globulin.	Caseinogen of cow's milk.	Gelatin.	Keratin, from horse hair.	Edestin, a globulin from cotton seed.	Zein, from maize.	Glutelin, from wheat.
Glycine . . .	0	0	3.5	0	25.5	4.7	3.8	0	0.02
Leucine . . .	20.0	6.1	18.7	10.5	7.1	7.1	2.9	18.6	5.6
Glutamic acid .	7.7	8.0	8.5	21.8	5.8	3.7	17.2	26.2	43.7
Tyrosine . . .	2.1	1.1	2.5	4.5	0	3.2	2.1	3.5	1.2
Arginine . . .	4.9	5.4	3.9	3.8	7.6	...	11.7	1.2	3.2
Tryptophan . .	+	+	+	1.5	0	...	+	0	1.0
Cystine . . .	2.5	0.3	0.7	0.06	... {	More than 10 }	0.2	...	0.4

Such numbers, of course, are not to be committed to memory, but they are sufficient to convey to the reader the differences between the proteins. There are several blanks left, on account of no accurate estimations having yet been made. Where the sign + occurs, the substance in question has been proved to be present, but not yet determined quantitatively. Among the more striking points brought out are:—

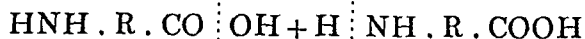
1. The small amount of glycine in albumins.
2. The high percentage of glycine in gelatin.
3. The absence of tyrosine, cystine and tryptophan in gelatin.
4. The high percentage of the sulphur-containing substance (cystine) in keratin.
5. The high percentage of glutamic acid in vegetable proteins.

Fischer discovered the way in which the amino-acids are linked together into groups. The groups are termed *peptides* or *polypeptides*; many of these have been made synthetically in the laboratory, and so the synthesis of the protein molecule is foreshadowed.

We may take as our examples of the peptides some of the simplest, and may write the formulæ of a few amino-acids as follows:—



Two amino-acids are linked together as shown in the following formula—



What happens is that the hydroxyl (OH) of the carboxyl (COOH) group of one acid unites with one atom of the hydrogen of the other amino (HNH) group, and water is thus formed, as shown within the dotted lines: this is eliminated and the rest of the chain closes up. In this way we get a *dipeptide*. Thus glycyl-glycine, glycyl-leucine, leucyl-alanine, alanyl-leucine, and numerous other combinations are obtained. If the same operation is repeated we obtain tripeptides (leucyl-glycyl-alanine, alanyl-leucyl-tyrosine, etc.); then come the tetrapeptides, and so on. In the end, by coupling the chains sufficiently often and in appropriate order, Fischer has already obtained substances which give some of the reactions of peptones.

The Structure of Proteins.—The evidence is now very complete that the amino-acids in a protein are not linked together in straight chains, although there is still some discussion as to what the actual arrangement is. Wrinch, a mathematician, has suggested a cycloid structure in which groups are united together in a somewhat similar way to the groups of a sterol, and has constructed three-dimensional models accordingly, but other workers prefer to consider them as long chains folded on themselves. Possibly both forms exist. (Ref. Lloyd and Shore.)

It is beyond the scope of this book to give details of estimation of individual amino-acids, but the following general methods of protein analysis may be given.

Hausmann's Method.—This is a short and trustworthy procedure, by which an approximate knowledge of the nitrogen distribution in the protein molecule is ascertained.

It is shortly as follows:—The whole nitrogen of the protein is estimated by Kjeldahl's method. A weighed amount is then hydrolysed by means of hydrochloric acid, and then the cleavage products are separated into three classes and the nitrogen estimated in each, as—

1. Ammonia nitrogen. This comprises the nitrogen of the protein molecule which is easily split off as ammonia, and is determined by distilling off the ammonia after adding magnesia.

2. Diamino-N. The fluid, free from ammonia, is precipitated by phosphotungstic acid, and the nitrogen present in the precipitate determined. This represents the nitrogen of the diamino-acids (lysine, arginine, etc.).

3. Mono-amino-N is then estimated in the residual fluid.

The method has proved useful for the differentiation of proteins, and interesting deductions as to their food value have been drawn from its results.

Van Slyke's Method.—In this method, the two last fractions in Hausmann's method are treated with nitrous acid, which liberates nitrogen from amino-groups. By measuring the nitrogen evolved, the amino-nitrogen is ascertained, and the non-amino-nitrogen (that is, the nitrogen in heterocyclic combination in proline, tryptophan, etc.) is determined by difference. This method can be worked with quite small quantities of protein, and from 98 to 100 per cent. of the nitrogen is accounted for.

CHAPTER XXI

PHYSICAL CHEMISTRY AND ITS BEARING ON PHYSIOLOGICAL PROBLEMS

THE investigations of physical chemists have given us new conceptions of the nature of solutions, and so are of importance in biological processes, especially on methods by which substances pass through membranes.

Water is the fluid in which soluble materials are usually dissolved. At ordinary temperatures it is a liquid the molecules of which are in constant movement; the hotter the water the more active are the movements of its molecules, until when at last it boils, the molecules leave the solution. Perfectly pure water consists of molecules H_2O with a very few H and OH ions. The water molecules undergo very little dissociation into their constituent ions, and it is for this reason that pure water is an extremely poor conductor of electricity.

If a substance such as sugar is dissolved in the water, the solution still remains incapable of conducting an electrical current. The sugar molecules in solution are still sugar molecules; they do not undergo dissociation.

But if a substance such as common salt is dissolved in the water, the solution is then capable of conducting electrical currents, and the same is true for most acids, bases, and salts. These substances do undergo **dissociation**, and the simpler units into which they are broken up in the water are called *ions*. Thus, if sodium sulphate is dissolved in water a certain number of its molecules become dissociated into sodium ions, which are charged with positive electricity, and sulphate ions, which are charged with negative electricity. Similarly, a solution of hydrochloric acid in water contains free hydrogen ions and free chlorine ions. Sulphuric acid is decomposed into hydrogen ions and ions of SO_4 . The term ion is thus not equivalent to atom, for an ion may be a group of atoms, such as SO_4 , in the example just given, and it always carries an electric charge.

Further, in hydrochloric acid, the negative charge of the chlorine ion is equal to the positive charge of the hydrogen ion; but in sulphuric acid the negative charge of the SO_4 ion is equal

to the positive charge of two hydrogen ions. We can thus speak of monovalent, divalent, trivalent, etc., ions.

Ions positively charged are called *kat-ions* because they move towards the kathode or negative pole; those which are negatively charged are called *an-ions* because they move towards the anode or positive pole. The following are some examples of each class:—

Kat-ions. Monovalent:— H^+ , Na^+ , K^+ , NH_4^+ , etc.

Divalent:— Ca^{++} , Ba^{++} , Fe^{++} (in ferrous salts), etc.

Trivalent:— Al^{+++} , Bi^{+++} , Sb^{+++} , Fe^{+++} (in ferric salts), etc.

An-ions. Monovalent:— Cl^- , Br^- , I^- , OH^- , NO_3^- , etc.

Divalent:— S^{--} , Se^{--} , SO_4^{--} , etc.

The ions liberated by the act of dissociation are, as we have seen, charged with electricity, and when an electrical current is led into such a solution, it is conducted through the solution by the movement of the ions. Substances which exhibit the property of dissociation are known as *electrolytes*.

The liquids of the body contain electrolytes in solution, and it is owing to this fact that they are able to conduct electrical currents.

This conception of electrolytic dissociation which we owe to Arrhenius is extremely important in relation to osmotic pressure, because the process of dissociation increases the number of particles moving in the solution, and so increases the osmotic pressure, for in this relation an ion plays the same part as a molecule.

It has been shown also that living tissues are extremely sensitive to the nature and the concentration of ions in their environment. Some of these facts, which we owe largely to the work of Ringer and of Loeb, we have already referred to in relation to the heart, amœba, and cilia.

Some substances like sodium chloride are fully dissociated, but others such as weak acids and bases and their salts are not fully dissociated but become more so when in dilute solution.

The Dissociation of Different Electrolytes.

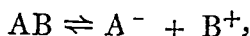
Strong Electrolytes.—A crystal of common salt consists of a closely packed orderly arranged mass of ions of sodium and chlorine. No particular sodium ion is attached to any particular chlorine ion. That is, the crystal is not made up of NaCl molecules but of Na^+ and Cl^- ions held together by the attractive forces due to their opposite charges.

When the sodium chloride is dissolved in water NaCl molecules

are not formed, the Na^+ ions and the Cl^- ions continue to lead separate existences.

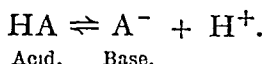
So far as is known SO_4^{--} and K^+ ions also belong to the class of completely dissociated electrolytes, and all salts are completely dissociated in weak solution.

Weak Electrolytes.—The dissociation of compounds in this group can be represented by the general equation

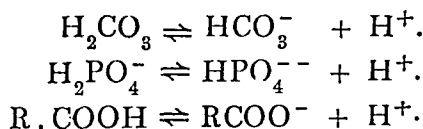


the dissociation obeying the law of mass action. Water, organic acids, proteins and some calcium and magnesium compounds all undergo partial reversible dissociation. The first three of these are of general importance and will be dealt with individually.

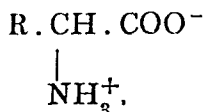
The Dissociation of Weak Acids.—An acid can be defined as any compound which can give rise to hydrogen ions, and a base as a compound which can take them up. The relationship between an acid and a base can then be expressed



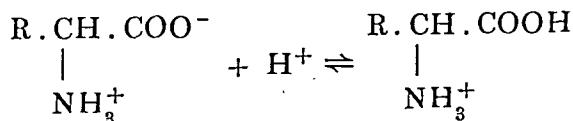
The chief acids of the body and the dissociation which they undergo at physiological $p\text{H}$ can be represented by the following:



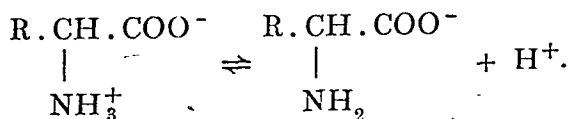
The Dissociation of Amino-Acids.—The *iso-electric point* of an amino-acid is defined as the $p\text{H}$ at which the total charge on the amino-acid is zero. In this state the constitution of the ordinary α -amino-acid can be represented by



If the $p\text{H}$ is less than the iso-electric point it can function as a base,



or if the $p\text{H}$ is greater than the iso-electric point, as an acid,



These doubly-charged ions which can function as acids or bases are known as zwitterions.

The Dissociation of Proteins.—Like the amino-acids, the iso-electric point of a protein is defined as the pH at which the total charge on the molecule is zero. In this condition the protein molecule carries many positively and negatively charged groups. The total charge is zero because the number of positive charges is equal to the number of negative charges. As in the case of the amino-acids, at pH 's greater than the iso-electric point the protein behaves as an acid and at pH 's below the iso-electric point as a base. (Taylor.)

Gramme-molecular Solutions.—From the point of view of osmotic pressure a convenient unit is the gramme-molecule. A gramme-molecule of any substance is the quantity in grammes of that substance equal to its molecular weight. A gramme-molecular solution is one which contains a gramme-molecule of the substance per litre. Thus a gramme-molecular solution of sodium chloride is one which contains 58.46 grammes of sodium chloride ($Na = 23.00$; $Cl = 35.46$) in a litre. A gramme-molecular solution of glucose ($C_6H_{12}O_6$) is one which contains 180 grammes of glucose in a litre. A gramme-molecule of hydrogen (H_2) is 2 grammes by weight of hydrogen, and if this was compressed to the volume of a litre, it would be comparable to a gramme-molecular solution. It therefore follows that a litre containing 2 grammes of hydrogen contains the same number of molecules of hydrogen in it as a litre of a solution containing 58.46 grammes of sodium chloride, or one containing 180 grammes of glucose, has in it of salt or sugar molecules respectively. To put it another way, the heavier the weight of a molecule of any substance, the more of that substance must be dissolved in the litre to obtain its gramme-molecular solution. Or still another way: if solutions of various substances are made all of the same strength per cent., the solutions of the materials of small molecular weight will contain more molecules of those materials than the solutions of the materials which have heavy molecules. We shall see that the calculation of osmotic pressure depends upon these facts.

Diffusion.—If two gases are brought together within a closed space, a homogeneous mixture of the two is soon obtained. This is due to the movements of the gaseous molecules within the confining space, and the process is called *diffusion*. This process, we have seen, is important in relation to the passage of gases to and from the blood in the lungs. In a similar way diffusion will effect in time a homogeneous mixture of two liquids or solutions. If water is carefully poured on to the surface of a solution of salt so as to form two layers, the salt or its ions will soon be equally distributed throughout the whole. If a solution of albumin or any other *colloidal*

substance is used instead of salt in the experiment, diffusion will be found to occur much more slowly.

Osmosis.

If, instead of pouring the water on to the surface of a solution of salt or sugar, the two are separated by a membrane made of such a material as parchment, a diffusion will occur, though more slowly than in cases where the membrane is absent. In time, the water on each side of the membrane will contain the same quantity of sugar or salt. Substances which pass through such membranes are called *crystalloids*. Substances which have large molecules (starch, protein, etc.) and do not pass through such membranes are called *colloids*. Very few, if any, membranes are equally permeable to water and to molecules of the substances dissolved in the water. If in fig. 127 the compartment A is filled

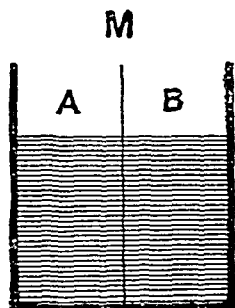


FIG. 127.

with pure water, and B with a sodium chloride solution, the liquids in the two compartments will ultimately be found to be equal in bulk as they were at the start, and each will be a solution of salt of half the strength of that originally in the compartment B. But at first the volume of the liquid in compartment B increases, because more water molecules pass into it from A than salt molecules pass from B to A. The term **osmosis** is generally limited to the stream of water molecules passing through a membrane, while the term **dialysis** is applied to the separation of those substances which can pass through a membrane from those which cannot. At first, then, since osmosis (the diffusion of water) is more rapid than the dialysis (the diffusion of the salt molecules or ions), the level of B becomes higher than that of A. This difference indicates the higher **osmotic pressure** of the salt solution or the power of the solution to attract water. If a bladder containing strong salt solution is placed in a vessel of distilled water, water passes into the bladder by osmosis, so that the bladder is swollen, and a manometer connected with its interior will show a rise of pressure (osmotic pressure).

The total osmotic pressure cannot, however, be measured in this way because (1) the salt diffuses out as the water diffuses in, and (2) the increased hydrostatic pressure in B (due to gravity) tends to interfere with the passage of the water to B (see Filtration below).

It is therefore necessary to use a membrane which will not allow salt to pass out either by dialysis or filtration, though it will let the water pass in. Such membranes are called *semi-permeable* membranes, and one of the best of these is ferrocyanide of copper. This

may be made by taking a cell of porous earthenware and washing it out first with copper sulphate and then with potassium ferrocyanide. An insoluble precipitate of copper ferrocyanide is thus deposited in the pores of the earthenware.

If such a cell is arranged as in fig. 128, and filled with a 1 per cent. solution of sodium chloride, water diffuses in, till the pressure registered by the manometer reaches the enormous height of 5000 mm. of mercury. If the pressure in the cell is increased beyond this artificially, water will be pressed through the semi-permeable walls of the cell and the solution will become more concentrated.

Though it is theoretically possible to measure osmotic pressure by a manometer in this direct way, practically it is hardly ever done, because it has been found difficult to construct a membrane which is absolutely semi-permeable; they are nearly all permeable in some degree to the molecules of the dissolved crystalloid. In course of time, therefore, the dissolved crystalloid will be equally distributed on both sides of the membrane, and osmosis of water will cease to be apparent, since it will be equal in both directions.

Calculation of Osmotic Pressure.—

As a simple example we may take a 1 per cent. solution of cane-sugar which does not dissociate into ions.

Two grammes of hydrogen at N.T.P. occupy a volume of 22.4 litres. A gramme-molecule of hydrogen—that is, 2 grammes of hydrogen—when brought to the volume of 1 litre, will exert a gas pressure equal to that of 22.4 litres compressed to 1 litre—that is, a pressure of 22.4 atmospheres. A

gramme-molecular solution of cane-sugar, since it contains the same number of molecules in a litre, must therefore exert an osmotic pressure of 22.4 atmospheres also. A gramme-molecular solution of cane-sugar ($C_{12}H_{22}O_{11}$) contains 342 grammes of cane-sugar in a litre of water. A 1 per cent. solution of cane-sugar contains only 10 grammes of cane-sugar in a litre; hence the osmotic pressure of

a 1 per cent. solution of cane-sugar is $\frac{10}{342} \times 22.4$ atmospheres, or 0.65 of an atmosphere, which in terms of a column of mercury = $760 \times 0.65 = 494$ mm.

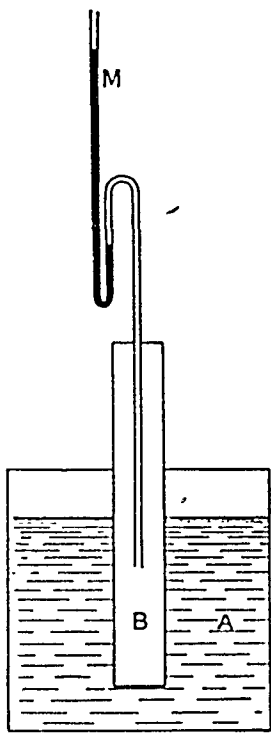


FIG. 128.—A, outer vessel, containing distilled water; B, inner semi-permeable vessel, containing 1 per cent. salt solution; M, mercurial manometer. (After Starling.)

It is not possible, however, to apply this method to mixed solutions containing electrolytes such as occur in the body since it is not known how many molecules are ionised.

Determination of Osmotic Pressure by means of the Freezing-point.—This is the method which is almost universally employed. The principle on which the method depends is the following:—The freezing-point of a solution of any substance in water is lower than that of water; the lowering of the freezing-point is proportional to the molecular concentration of the dissolved substance, and that, as we have seen, is proportional to the osmotic pressure.

When a gramme-molecule of any substance is dissolved in a litre of water, the freezing-point is lowered by 1.87°C. , and the osmotic pressure is, as we have seen, equal to 22.4 atmospheres, that is, $22.4 \times 760 = 17,024$ mm. of mercury.

We can, therefore, calculate the osmotic pressure of any solution if we know the lowering of its freezing-point in degrees Centigrade; the lowering of the freezing-point is usually expressed by the Greek letter Δ . The determination is made by the use of the Beckmann thermometer.

$$\text{Osmotic pressure} = \frac{\Delta}{1.87} \times 17,024.$$

For example, a 1 per cent. solution of sugar would freeze at -0.052°C. ; its osmotic pressure is therefore $\frac{0.052 \times 17,024}{1.87} = 473$ mm., a number approximately equal to that we obtained by calculation.

Mammalian blood serum gives $\Delta = 0.56^{\circ}\text{C.}$ A 0.9 per cent. solution of sodium chloride has the same Δ ; hence serum and a 0.9 per cent. solution of common salt have the same osmotic pressure, or are *isosmotic*. The osmotic pressure of blood serum is $\frac{0.56 \times 17,024}{1.87} = 5000$ mm. of mercury approximately, or a pressure of nearly 7 atmospheres.

The osmotic pressure of solutions may also be compared by observing their effect on red blood-corpuscles, or on vegetable cells such as those in *Tradescantia*. If the solution is *hypertonic*, i.e. has a greater osmotic pressure than the cell contents, the protoplasm loses water and shrinks, or if red corpuscles are used, they become crenated; if the solution is *hypotonic*, i.e. has a smaller osmotic pressure than the material within the cell-wall, and if red corpuscles are used they swell and burst. *Isotonic* solutions, such as physiological or normal salt solution, produce neither of these effects, because they have the same osmotic pressure as the material within the

cell-wall. Isosmotic solutions may or may not be isotonic, depending on their nature.

The Nature of Osmotic Pressure.—The following simple explanation is perhaps the best, and may be rendered most intelligible by an example. Suppose we have a solution of sugar separated by a semi-permeable membrane from water; that is, the membrane is permeable to water molecules, but not to sugar molecules. The streams of water from the two sides will then be unequal; on one side we have water molecules striking against the membrane in what we may call normal numbers, while on the other side both water molecules and sugar molecules are striking against it. On this side, therefore, the sugar molecules take up a certain amount of room, and do not allow the water molecules to get to the membrane; the membrane is, as it were, screened against the water by the sugar, therefore fewer water molecules will get through from the screened to the unscreened side than *vice versa*. This comes to the same thing as saying that the osmotic stream of water is greater from the unscreened water side to the screened sugar side than it is in the reverse direction. The more sugar molecules that are present the greater will be their screening action, and thus we see that the osmotic pressure is proportional to the number of sugar molecules in the solution, that is, to the concentration of the solution.

Osmotic pressure is, in fact, equal to that which the dissolved substance would exert if it occupied the same space in the form of a gas (van 't Hoff's hypothesis). The nature of the substance makes no difference; it is only the number of molecules which causes osmotic pressure to vary. The osmotic pressure, however, of substances like sodium chloride, which are electrolytes, is greater than what one would expect from the number of molecules present. This is because the molecules in solution are split into their constituent ions, and an ion plays the same part as a molecule, in questions of osmotic pressure. In dilute solutions of sodium chloride ionization is complete, and as the total number of ions is then nearly double the number of original molecules, the osmotic pressure is nearly double what would have been calculated from the number of molecules.

The analogy between osmotic pressure and the pressure of gases is very complete, as may be seen from the following statements:—

1. At a constant temperature osmotic pressure is proportional to the concentration of the solution (Boyle-Mariotte's law for gases).
2. With constant concentration, the osmotic pressure rises with and is proportional to the temperature (Gay-Lussac's law for gases).
3. The osmotic pressure of a solution of different substances is equal to the sum of the pressures which the individual substances would exert if they were alone in the solution (Henry-Dalton law for partial pressure of gases).
4. The osmotic pressure is independent of the nature of the substance in solution, and depends only on the number of molecules or ions in solution (Avogadro's law for gases).

Filtration.—Fluids may also pass through membranes in virtue of a mechanical or hydrostatic difference in pressure on the two sides. The membrane leaks, as it were, but only the substances in solution pass through. This occurs in the case of ordinary filtration through a piece of blotting-paper. It is, however, important to note that the concentration of the filtrate is the same as that of the true solution before filtration.

Physiological Applications.—It will at once be seen how important all these considerations are from the physiological standpoint. In the body we have aqueous solutions of various substances separated from one another by membranes. Thus there are the

endothelial walls of the capillaries separating the blood from the lymph; the epithelial walls of the kidney tubules separating the blood and lymph from the urine; and similar epithelium in all secreting glands; there is also the wall of the alimentary canal separating the digested food from the blood-vessels and lacteals. In such important problems as lymph-formation, the formation of urine and other excretions and secretions, and the absorption of food, we have to take into account the laws which regulate the movements both of water and of substances which are held in solution by the water. In the body osmosis and filtration both take place. Further complicating these two processes there is another force, namely, the secretory or selective activity of the living cells of which membranes are composed. This is sometimes called by the name **vital action**, which is an unsatisfactory and unscientific expression. The laws which regulate filtration, diffusion, and osmosis are fairly well known and can be experimentally verified. But we have undoubtedly some other force, or some other manifestation of force, in living membranes. It probably is some physical or chemical property of living matter which has not yet been brought into line with the known chemical and physical forces which operate in the inorganic world. We cannot deny its existence, for it sometimes operates so as to neutralise the known forces of osmosis and filtration.

The more one studies the questions of lymph-formation and glandular secretion, the more it is evident that mere osmosis and filtration will not explain them entirely. The basis of the action is no doubt physical, but the living cells do not behave like the dead membrane of a dialyser; they have a selective action, picking out some substances and passing them through, while rejecting others. This is in part, but not wholly, due to the fact that the **permeability** is greater to some ions than to others. The subject has been extensively investigated by Hamburger.

The cell has no real choice in what shall pass through and what be kept back. It has been found that different ions modify in various ways the normal permeability. The electric charge of the ions must be an important factor in determining the passage of substances through the cell and its plasmatic membrane. This permeability may become altered in diseased conditions by an upset of the normal relationships of the ions, hence cellular activity becomes abnormal. Electric charge, moreover, is only one factor; molecular size in passing the sieve-like membrane is another; solution affinities, surface tension, etc., are still others.

These considerations may be exemplified by what is known in relation to the permeability of cells to glucose. This sugar is always present in the blood in health, but is wholly contained in the plasma; the corpuscles are stated to be impermeable to this variety

of sugar. In diabetes they become permeable. (See also Secretion and Absorption.)

The theory of diffusion of dissolved substances through membranes as applied to cells has been profoundly influenced by the discovery of the composition of the cell-wall. At one time it was believed that diffusion of a colloid material was prevented by the pores of the membrane being too small to allow large molecules to get through them; it was thought to act as a sort of sieve. But this cannot be the whole explanation, and it is now held that *solution affinities* play a most important part; that is to say, a membrane is permeable to substances which are soluble in the material of the membrane. Such solubility may imply the formation of actual chemical unions or more frequently the process is one of adsorption (see below); this latter process comes specially into play when nutritive materials are assimilated by the cell by means of the protein solution which occupies the interstices between the fat molecules of the membrane. On the other hand, the permeability by substances such as alcohol, chloroform, and ether, is mainly determined by the solubility of these materials in the fatty or fat-like components of the membrane, and this consideration is the foundation of the Meyer-Overton theory of the narcotic effect on cells which these volatile anæsthetics exercise.

The process of absorption depends largely, but not entirely, on physical principles. Distilled water and readily diffusible substances readily pass through into the blood and lymph, but if hypertonic saline is introduced into the intestine, water passes from the blood to the intestine. This is the action of a purgative, especially the sulphates, which are not so readily absorbed as chlorides. Curiously, however, as Waymouth Reid has shown, if the living epithelium of the intestine is removed, absorption comes very nearly to a standstill, although from the purely physical standpoint removal of the thick columnar epithelium would increase the facilities for osmosis and filtration.

The osmotic pressure exerted by crystalloids is very considerable, but their ready diffusibility limits their influence on the flow of water in the body. Thus if a strong solution of salt is injected into the blood, the first effect will be the setting up of an osmotic stream from the tissues to the blood. The salt, however, would soon diffuse out into the tissues, and would now exert osmotic pressure in the opposite direction. Moreover, both effects will be but temporary, because excess of salt is soon got rid of by the excretory organs.

Osmotic Pressure of Proteins.—The osmotic pressure of proteins is of special importance in relation to the blood, where they have been shown by Starling to exert a pressure of 30 mm. of mercury. By means of this pressure it is possible to explain the fact that an

isotonic or even a hypertonic solution of a diffusible crystalloid may be completely absorbed from the peritoneal cavity into the blood. The pressure observed may be due to saline materials from which it is difficult to separate proteins.*

The functional activity of the tissue elements is accompanied by the breaking down of their protein constituents into such simple materials as urea (and its precursors), sulphates and phosphates. These materials pass into the lymph, and increase its molecular concentration and its osmotic pressure; thus water is attracted (to use the older way of putting it) from the blood to the lymph, and so the volume of the lymph rises and its flow increases. On the other hand, as these substances accumulate in the lymph they will in time attain there a greater concentration than in the blood, and so they will diffuse towards the blood, by which they are carried to the organs of excretion.

But, again, we have a difficulty with the proteins: they are most important for the nutrition of the tissues, but they are practically indiffusible. We must therefore assume that their presence in the lymph is due somehow to filtration from the blood.

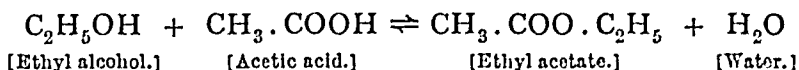
It is the osmotic pressure of the protein which is chiefly responsible for preventing the fluid of the blood from leaving the blood-vessels.

In the capillaries we have a balance of pressure: on the one hand we have the pressure of the blood, together with the osmotic pressure of the tissue fluids, tending to suck fluid from the vessels; while, on the other hand, this is counteracted by the osmotic pressure of the blood which is exerted by the salts and proteins. The balance is, however, a very delicate one; since an increase of capillary pressure causes fluid to pass into the tissues (*œdema*)—and hence it is that our feet are slightly larger at the end of the day. On the other hand, when the capillary pressure falls, as in hæmorrhage, fluid passes from the tissues into the blood. In kidney disease, when much protein, especially serum albumin, which has a smaller molecule and higher osmotic pressure than serum globulin, is lost in the urine, *œdema* is apt to occur, and is in part due to loss of colloid.

The Law of Mass Action.—This law is of fundamental importance in relation to the processes which break down substances in digestion and subsequently cause the products to be built up into the tissues of the body. The law states that the rate at which a reaction takes place is proportional to the mass of the reagents in a certain volume, or, more accurately, to the concentration of

* Bayliss has shown that the saline constituents found in a native protein are not mechanically mixed with it, and are also not in true chemical combination with it, but are in a condition intermediate between these two extremes, to which the term *adsorption* is applied. Many dyes used for staining fabrics and histological preparations are also adsorbed.

the active masses of the reagents (Bayliss). In a reversible reaction the extent to which either will proceed will similarly depend on the concentration of the reagents on either side. In the equation



the extent to which alcohol and acetic acid will be formed, *i.e.* the *equilibrium-point*, in such a hydrolysis will depend on the concentration of water, and of the other reacting constituents. (See p. 308.)

In a test-tube, therefore, the hydrolysis of a starch or of a protein by an enzyme is not quite complete, some of the substances always remaining unchanged.

In the body, however, some of the substances produced are removed from the sphere of reaction. In the digestion of starch, for example, the soluble sugar formed becomes absorbed and no longer interferes with the continuance of the reaction.

Similarly, in the blood and tissues one of the substances, the glycogen, is also removed from the sphere of reaction and the synthesis can, therefore, proceed. It is not yet quite clear how some of the substances are actually removed from the sphere of the reaction, but that such a process does take place seems tolerably certain.

Surface Tension.—The surface layer of a liquid possesses certain properties which are not shared by the rest of it, for in the interior the arrangement of matter is symmetrical round any point, whereas on the surface the surroundings consist of liquid on one side only, while on the other side is solid, or gas, or it may be another liquid. In a gas, the molecules are free from one another's attractive influence and fly about freely with high velocity, producing pressure on the walls of the containing vessel; in a liquid, the mutual attractions of the molecules are great enough to keep the substance together in a definite volume; in order to separate the molecules and convert the liquid into gas a large amount of energy is required—the so-called latent heat of vaporisation. The molecular attractions in a liquid are thus very great, so that a molecule of the surface layer is pulled strongly inwards, and this layer constitutes a stretched elastic skin, and the power thus exerted is spoken of as *surface tension*. The effect of surface tension is most simply seen in a free drop of liquid, such as a rain-drop, or a drop of oil immersed in a mixture of alcohol and water of the same density. There is then nothing to prevent the tension in the surface layer from contracting as much as possible, and the drop will therefore assume

a form in which its volume will have the smallest surface, that is, the drop will assume the form of a sphere.

Now animal cells are liquid, and when they are at rest, other forces being absent, they also are spherical, and although they do not possess, as a rule, a definite wall of cellulose or other hard substance such as vegetable cells have, nevertheless the surface film, exercising the force called surface tension, plays the part of an elastic skin, and is termed the *plasmatic membrane*. This membrane plays an important physiological rôle. In the projection of pseudopodia, for instance, variations in the surface tension must occur in different parts of the periphery of the cell. Protoplasm, however, is not a simple liquid, but contains substances of varying chemical composition, and substances which have the power of diminishing surface tension always show a tendency to accumulate at the surface. Hence the fats and lipides which are powerful depressants of surface tension are found, probably in a state of an extremely fine emulsion, more abundantly in the plasmatic membrane than elsewhere in the cell.

Adsorption.—From what has been said above it is evident that any substance in solution in a liquid in contact with a surface will be concentrated on that surface. This process is called adsorption. The power of charcoal to take up gases or dyes is due to the large surface it presents. For a similar reason the amount of congo-red which a filter-paper will take up is relatively *greater* the more dilute the solution of the dye. We shall see that this concentration at surfaces is important in digestion by enzymes which are colloids and have therefore an extremely large surface on which dilute acids and alkalis may be looked upon as becoming concentrated and having therefore the activity of strong solutions.

Colloidal Solutions.—The study of colloids is important, seeing how many important physiological substances belong to this class; for instance, the proteins, and polysaccharides. Their main characters are, that they do not pass through a parchment membrane (p. 295), their solutions are opalescent, they crystallise with difficulty if at all, they have a tendency to form jellies (*e.g.*, gelatin), or to coagulate under the influence of heat and other agents (as is the case with most proteins), and they exert a low osmotic pressure. Inorganic substances (*e.g.*, several metals, and compounds such as silicic acid) may also assume a colloidal condition; these are in an unstable physical condition, passing from the "sol" (or fluid) to the "gel" (or jelly-like) condition under slight provocation. This confers upon them their power to act as *catalysts*.

The solutions formed by colloidal materials are not true solutions. They are really suspensions of very minute particles. The particles, though ordinarily invisible, will nevertheless scatter

light, just as minute dust particles in the air are lit up by a beam of sunlight (Tyndall phenomenon). If a beam of light is passed through a colloidal solution the particles may be seen by means of a microscope. This principle is used in the ultra-microscope.

Reaction of Fluids.—Although this important subject is really part of physical chemistry, it is more conveniently considered in connection with the maintenance of body reaction as a whole in a later chapter.

Enzymes.

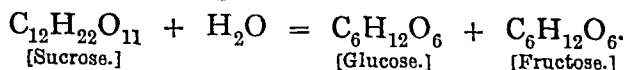
In all living things there take place a large number of chemical reactions which are characterised by a rapidity and completeness which is quite unexpected considering how difficult it is to bring about similar reactions outside the body by ordinary chemical reagents.

This is made possible by the existence of colloidal organic catalysts known as *enzymes*, so called because they were first found in yeast. They are also called ferments because those in yeast cause *fermentation*, that is frothing and bubbling, due to the breakdown of carbohydrate into alcohol and carbon dioxide. Like all catalysts they are not used up in the reaction—"A little leaven leaveneth the whole lump"—but there is now evidence that some act by entering into chemical combination temporarily with the *substrate* or substance on which they act and then separating off again.

Some enzymes normally act extra-cellularly and exist, for example, in the digestive secretions of the alimentary canal, where they play an important part in the breakdown of foodstuffs, but intracellular enzymes are also present in all cells. We are familiar with the existence of enzyme action outside the body. Enzymes are present in the bacteria which bring about the souring of milk, and are the active agents in the processes of putrefaction whether autolytic or caused by micro-organisms. After breaking up the cells or bacteria it is possible to extract the enzymes and it is found that they act apart from the cell. It is often possible to reduce the enzyme to a powder form which will keep for a considerable time. In several instances enzymes have been crystallised, *e.g.* pepsin, trypsin, urease.

We may classify enzymes according to the kinds of chemical reactions they catalyse or according to the substrates upon which they act. Modern usage is to name the enzyme by adding *-ase* to the appropriate substrate, but the older ones retain their original names.

Hydrolytic enzymes activate the addition of water to the substrate which then breaks up into simple molecules, *e.g.*



They bring about the digestion of food in the alimentary canal and are further discussed under digestion.

There are several varieties of hydrolytic enzymes and it will be noted that as a rule enzymes act in groups towards a common end.

The first enzyme to be discovered was the hydrolytic enzyme, diastase of barley, which was shown by Kirchhoff in 1814 to convert starch into sugar in the brewing of beer. The next, the pepsin of the gastric juice, which hydrolyses protein was found by Schwann in 1836.

1. **Carbohydases** which hydrolyse carbohydrates, *e.g.* those which convert polysaccharides (starch, glycogen) into sugar with intermediate dextrins. Examples: the *diastase* of vegetable seeds, and the *ptyalin* of saliva.

There are also those which convert disaccharides into monosaccharides, *e.g.* *invertase* of yeast cells; *invertase* of intestinal juice; these convert sucrose into equal parts of glucose and fructose while maltase and lactase break down maltose and lactose respectively.

2. **Proteases** which split proteins into proteoses, peptones, polypeptides, and finally amino-acids. Examples: the *pepsin* of gastric, the *trypsin* of pancreatic juice, and the *erepsin* of intestinal juice. They are contained also in the phagocytic cells of the blood and tissues, where they digest and destroy bacteria. They hydrolyse the C—N link of proteins.

Esterases hydrolyse the ester link, *i.e.* between an acid and an alcohol. They include:—

1. *Lipases*, which are present in the pancreatic and gastric juices, and which hydrolyse the glycerides of the higher fatty acids in the small intestine.

2. *Phosphatases* or *phosphoric esterases*, which facilitate the precipitation of calcium in the bone and are present in the kidney and stomach, hydrolyse the link between H_3PO_4 and the OH group of a large number of compounds, such as phosphatides, hexose phosphate, etc.

3. *Lecithinases* which act on lecithins.

4. *Esterases*, which hydrolyse the esters of the lower fatty acids and of choline and betaine. The best known is the choline esterase of the blood, which destroys acetyl-choline.

Oxidation-Reduction Enzymes.—These enzyme systems are closely related to the actions of the vitamin B_2 complex, especially nicotinic acid and thiamine.

Oxidases.—These are not hydrolytic, but are oxygen carriers and produce oxidation; they are mainly found as intracellular enzymes, and are discussed in relation to tissue respiration.

Reductases.—These are the counterpart of the oxidases, and produce reduction in the tissues.

Miscellaneous Enzymes.

1. *Deaminases*—these remove the amino-group from the amino-compounds, and are found in the liver.

2. *Coagulative Enzymes*—those which convert soluble into insoluble proteins; the best example of this class is *rennet* or *rennin*, found in the gastric juice; it converts the soluble caseinogenate of milk into casein. This is the substance used by cooks to make curds and whey. *Thrombase* in the blood catalyses blood coagulation.

There are also a number of unclassified enzymes, such as *carbonic anhydrase*, which facilitates the giving up of carbon dioxide by the blood in the lungs.

Characteristics of Enzyme Action.

Zymogens.—These are the parent substances or precursors of the enzymes. The granules seen in many secreting cells consist very largely of zymogen, which in the act of secretion is converted into the active enzyme. Thus, pepsin is formed from pepsinogen, trypsin from trypsinogen, and so forth.

Activation of Enzymes. Co-enzymes.—Many enzymes contained in secretions are in a condition ready for action. In other cases this is not so, and their action occurs only after they have been rendered energetic by the presence or action of other substances, termed activating agents, or kinases and co-enzymes. Sometimes the activator is an inorganic substance, such as calcium for thrombin, chloride for ptyalin, or magnesium for phosphatase. The action of a kinase is irreversible, but it is possible to remove the co-enzyme from its sphere of action and temporarily inactivate an enzyme. Co-enzymes are of special importance in the oxidation-reduction systems inside cells.

The Specificity of Enzyme Action.—In most cases the action of an enzyme is extraordinarily limited; thus there are three separate enzymes to hydrolyse the three principal disaccharides, sucrose, lactose, and maltose, neither of which will act upon either of the other two sugars in the list. Arginase splits arginine into ornithine and urea, but will act upon no other substance. The "lock and key" simile first introduced by Emil Fischer will aid us in understanding this specificity of action, but it is becoming increasingly evident that this specificity depends on definite chemical reactions

For example, some enzymes will only act if the protein or polypeptide concerned has free NH_2 or COOH groups. If these are fixed by adding H or by esterification respectively, the enzyme loses its activity. The activity may also depend on the exact method by which the amino-acids, for example, of a protein are linked together, for an enzyme may act on a tripeptide and yet be incapable of acting on a corresponding dipeptide which has one less amino-acid.

Enzymes may then be considered as chemical complexes stabilised and made permanent by a colloidal carrier, or it may be that they are like polypeptides and composed of long complex chains.

The Inexhaustibility of Enzymes.—A small amount of enzyme will act on an unlimited amount of substrate, provided sufficient time is given, and provided also the products of action are removed. The enzyme appears to take a share in intermediate reactions, and there is some evidence that in certain stages it combines with the substrate; but subsequently when the substrate breaks up into simpler materials, the enzyme is liberated unchanged, and so ready to act similarly on a fresh amount of substrate.

The simple logarithmic law of enzyme action has been demonstrated for the majority of enzymes (invertase, trypsin, erepsin, lipase, etc.). The effect in a given time is proportional to the quantity of enzyme present.

Conditions affecting the Velocity of Enzyme Action.

These conditions have been aptly described as those which would affect the activity of slugs attacking a strawberry.

Concentration of Enzyme.—The more enzyme there is present the more rapidly will the action proceed; that is, provided the enzyme is thoroughly mixed with the substrate and has full opportunity of attacking it. The reaction is indeed dependent on the total surface offered to the enzyme. No doubt if we chopped up the strawberry the slugs could eat it more rapidly.

Concentration of Substrate.—The more substrate present the greater the speed of reaction, but there is an optimum concentration above which the action is slowed down.

The Effect of Temperature on Enzyme Action.—As the temperature rises the velocity of the action increases, until a temperature is reached at which the activity is greatest. Most enzymes act best at 40°C ., but there are exceptions; malt diastase, for instance, acts best at 60°C . Beyond the optimum temperature a further rise inhibits activity, until a temperature is reached when the enzyme is destroyed. The fatal temperature as a rule is in the neighbourhood of 50°C .

This statement, however, requires some modification, as whether

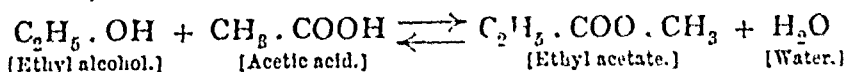
or not an enzyme is destroyed by a given temperature depends on the reaction of the medium in which it is. Boiling trypsin in an acid medium (Mellanby) in which, however, it is inactive does not destroy it, but it is readily destroyed in an alkaline medium, and pepsin may be boiled in neutral salt-free solution without loss of potential activity (Northrop).

The effect of a rise of temperature is complex, and is of a twofold nature. In the first place, and between certain limits, the law of Arrhenius is followed; that is, a rise of 10° doubles or even trebles the velocity of the action of the enzyme, as it does other chemical reactions. But as the temperature rises the velocity of disintegration of the enzyme also rises. The optimum temperature is that at which the enzyme work is best done; this is a temperature at which the accelerating effect is at its maximum, and the retarding effect due to enzyme destruction is not so great as to neutralise the accelerating effect.

Optimum Reaction of Enzyme Activity.—Some enzymes act best in an acid, others in an alkaline medium. For each there is an optimum hydrogen-ion concentration. If placed in an unsuitable medium they are not only inactivated but may be destroyed.

Removal of Products of Reaction.—Unless the products of reaction are removed they eventually hold it up in virtue of the law of mass action. In digestion, however, the enzyme actions tend to be very complete as the products are absorbed into the blood.

Reversibility of Enzyme Action.—In some cases the action of enzymes may be reversible. The majority of enzyme reactions are unimolecular, or reactions of the first order; that is to say, one substance only, the substrate, undergoes transformation; the other substance, the enzyme, does not alter in concentration. The law followed in such reactions is therefore the simple logarithmic law. But in these transformations we meet with the peculiarity that the reaction is not quite complete. A certain quantity of the substrate never disappears. This phenomenon is due to the fact that two reactions are always taking place in opposite directions. Simultaneously with the splitting up, the synthetic reaction begins, and synthesis or building up increases in proportion as the splitting of the compound advances. The velocity of the splitting process decreases at the same rate as the velocity of the synthetic process increases. At a certain point, both have the same velocity, and therefore no further change occurs in the mixture when this condition of equilibrium is reached. This rule is expressed by writing the chemical equation connected by a double arrow instead of the sign of equation, as follows:



This phenomenon is termed "*reversibility*." Commonly, however, the reaction is complete because its products are removed as soon as formed.

In intracellular action this is a factor of importance, for the same enzyme in the presence of different proportions of the substrate and its cleavage products may both build up and break down the same substance.

There are many instances of reversible activity in the body, such as the building up of starch (glycogen) and of protein and their subsequent breakdown. It is, however, by no means certain that the same enzymes are concerned in both processes.

The action of lipase, maltase, pepsin, trypsin, phosphatase have all been shown to be reversible, but the amount of substances formed have so far been very small, possibly because the exact conditions for their synthetic action are not sufficiently known.

Nature of Enzyme Action.—As has already been said, an enzyme may be considered to exercise a catalytic action. That is to say, the presence of the enzyme induces a chemical reaction to occur rapidly, which in its absence also occurs, but so slowly that any action at all is difficult to discover. To use the technical phrase, its action is to increase the *velocity* of chemical reactions. It is, for instance, quite conceivable that, if starch and water are mixed together, the starch will in time take up the water and split into its constituent molecules of sugar. But an action of this kind would be so slow, occupying perchance many years, that for practical purposes it does not take place at all. If an inorganic catalyst is added, such as sulphuric acid, and the temperature raised to boiling-point, the action takes place in a few minutes; if an organic catalyst, such as the enzyme ptyalin, is added, the velocity of the change is even greater; but, what is of more importance for the well-being of the animal, a moderate temperature, namely that of the body, amply suffices.

Various theories have been brought forward to account for this catalytic action, but there is as yet no certainty. It used to be thought that enzymes formed adsorption compounds with the substances they act upon but as indicated in relation to their specificity (p. 306) it now appears more likely that they form definite chemical combinations which permit the substrate to react more freely with other substances, *e.g.* water in the case of the hydrolytic enzymes.

The Nature of Enzymes.—Although, as we have said, enzymes are necessary for life, they are not themselves living; indeed, many of them have now been obtained in crystalline form, although this is not looked upon now as being necessarily inanimate. This is true of the well-known digestive enzymes, pepsin, trypsin, and amylase, and also of the enzyme urease which hydrolyses urea. In many cases the enzymes are derived from inactive precursors in the body.

cells known as *zymogens*, and in many instances the crystalline form of the precursor is different from that of the active enzyme.

All the crystalline enzymes which have been prepared so far are proteins, but some are active in solutions so dilute that no test for proteins can be obtained. It would seem that the activity depends on some peculiar arrangement of their amino-acids, but what this is has so far eluded discovery (Northrop).

In the case of certain oxidation-reduction systems, one of the essential constituents of the enzymes has been found to be a vitamin; for example, vitamin B pyrophosphate is co-carboxylase, which is necessary for the conversion of pyruvic acid to acetaldehyde. Riboflavine, a part of vitamin B₂, is a constituent of the yellow enzyme system necessary for the oxidation of hexose monophosphoric acid. Nicotinic acid is part of the co-enzyme of yeast juice which will activate dried yeast. Most enzyme action is very economical and leads to little or no evolution of heat, but of course this does not refer to the oxidases. A very large number of body processes depend on such action; indeed, it is very difficult to see how life could continue without them.

Finally, it may be said that it is never possible to demonstrate the presence of an enzyme except in the presence of its substrate, and it is just possible that the substrate itself plays some part in its formation and activation.

Enzyme Poisons.—Enzyme systems can be “poisoned” by numerous substances, notably mercury, silver, and gold, and to a lesser extent copper, zinc, and lead, by strong acids and alkalis, formaldehyde, cyanides. The toxic effects of these substances in man may in part be due to this action. Generally the poisons are protein precipitants. Enzymes are usually inactivated by ultra-violet light.

Anti-enzymes.—If an enzyme is injected into an animal its blood develops a substance known as an anti-enzyme which prevents the enzyme action. Substances such as anti-pepsin, anti-rennin, and anti-trypsin can be produced, and it is thought that such substances may play a part in preventing intestinal worms and even in protecting the cells lining the alimentary canal from being digested. The anti-enzymes are specific to individual enzymes.

Autolysis.—All dead tissue eventually digests itself and becomes liquid, and often this is assisted by bacterial digestion, as in the case of pus formation. A similar function of the autolytic action of enzymes is presumably concerned when the body lives on itself, thereby losing weight in starvation and fever. These enzymes are intracellular and may belong to any of the groups of hydrolytic enzymes. It seems probable that they play a part in the normal metabolism of living cells.

CHAPTER XXII

THE BLOOD

THE blood has a number of important functions in the body, some of which have already been studied. They are (1) Transport of substances from one part of the body to another, and in so doing it plays an important part in (2) Nutrition, (3) Respiration and (4) Excretion, and in the maintenance of the (5) Acid-base equilibrium. It also plays an important part in (6) the water balance of the body and (7) in the protection of the body against invasion by abnormal substances or by bacteria.

Blood is a somewhat viscid fluid, and in man and in all other vertebrate animals, with the exception of two,* is red in colour. It consists of a yellowish fluid, called **plasma** or **liquor sanguinis**, in which are suspended numerous **blood-corpuscles**, the majority of which are coloured, and it is to their presence that the red colour of the blood is due. They form 45 per cent. of the blood volume.

Even when examined in very thin layers, blood is *opaque*, on account of the different refractive powers possessed by its two constituents, the plasma and the corpuscles. On treatment with ether, water, and other reagents, however, it becomes transparent and assumes a lake colour, in consequence of the colouring matter of the corpuscles having been discharged into the plasma. The average *specific gravity* of blood at 15° C. (60° F.) varies from 1055 to 1062. A rapid and useful method of estimating the specific gravity of blood was invented by Roy. Drops of blood are taken and allowed to fall into fluids of known specific gravity. When the drop neither rises nor sinks in the fluid it is taken to be of the same specific gravity as that of the standard fluid. In Hammerschlag's method the drop is placed in a mixture of chloroform and benzene; more chloroform or benzene is added until the drop neither falls nor sinks, *i.e.* until the mixture has the same specific gravity as the blood; the specific gravity of the mixture is then taken. The *taste* is saltish. Its *temperature* varies slightly, the average being 37·8° C. (100° F.). The blood-stream is warmed by passing through the muscles and glands, but it is somewhat cooled on traversing the capillaries of the skin. Recently-drawn blood has a distinct *odour*, which in many cases is

* The *amphioxus* and the *leptocephalus*.

characteristic of the animal from which it has been taken; it may be further developed by adding to blood a mixture of equal parts of sulphuric acid and water. The *reaction* of the blood is faintly alkaline and is dealt with in a later chapter.

Blood Volume.—The quantity of blood in an animal may be estimated in the following manner:—A small quantity of blood is taken from an animal by venesection; it is defibrinated and measured, and used to make standard solutions of blood. The animal is then rapidly bled to death, and the blood which escapes is collected and defibrinated by whipping. The blood-vessels are next washed out with saline solution until the washings are no longer coloured, and these are added to the previously withdrawn blood; lastly, the whole animal is finely minced with saline solution. The fluid obtained from the mincings is carefully filtered and added to the diluted blood previously obtained, and the whole is measured. The next step in the process is the comparison of the colour of the diluted blood with that of standard solutions of blood and water of a known strength, until it is discovered to what standard solution the diluted blood corresponds. As the amount of blood in the corresponding standard solution is known, as well as the total quantity of diluted blood obtained from the animal, it is easy to calculate the absolute amount of blood which the latter contained, and to this is added the small amount which was withdrawn to make the standard solutions. Such experiments have shown that, although there is considerable variation, the blood volume of the dog is about $\frac{1}{12}$ to $\frac{1}{14}$ of the body-weight.

The application of the method to decapitated criminals has given values from $\frac{1}{8}$ to $\frac{1}{14}$. For the estimation of blood volume in **man** during life it is evident that other methods are necessary. These methods consist in adding a known amount of an easily recognisable substance to the circulating blood, and after thorough admixture a small known quantity of blood is withdrawn, and the substance estimated in it. Then by calculation, the total quantity of blood capable of holding all the foreign matter introduced is calculated.

The estimation of the blood volume in the living man is, however, fraught with difficulties. The methods commonly in use involve the injection of dyes usually "vital red" or "Evans blue."

The subject is of some practical interest as it is found that it may vary in disease. In talking of blood volume it should be realised that we really usually mean **plasma volume** as the dye does not enter the corpuscles (see Rowntree and Brown, 1929).

The following method is that now most extensively used. Two samples of blood (5 c.c.) are withdrawn and oxalated. A 1.5 per cent. solution of the dye is injected into an arm vein—after five minutes samples of blood are withdrawn and centrifuged. The

colour is compared, the tint of the dye in the plasma compared with standards consisting of uncoloured plasma and dye solutions of known concentrations. This method gives a total blood volume of from $\frac{1}{11}$ to $\frac{1}{14}$ of body-weight. In an average man the amount is then about **6 litres**, but this may be increased as in anæmia or at high altitudes. Similar results have been obtained by studying the change in blood concentration which occurs when plasma is injected.

All methods depending on the dilution of an injected substance have the disadvantage that they measure only the circulating volume of blood and not necessarily that available in the blood-depôts, which may or may not be full at the time of the estimation. Any state which causes them to contract, such as excitement and some diseases, may upset results when they are most needed, but in the same individual at rest repeated examinations under uniform conditions give reasonably constant results, the experimental error being quite small.

The Regulation of Blood Volume.—The blood volume obviously depends ultimately on the water content of the body as a whole; but even when conditions arise which tend to change it, a very considerable effort on the part of the body is needed to keep it approximately constant. This is done by the fluid passing through the capillary walls in either direction according to requirements. Thus the loss or the injection of small quantities of fluid changes the blood volume for only a short time, the factors which determine the direction of the flow of fluid being the capillary pressure and osmotic pressure of the blood. The subject is closely related to the water-balance of the body and to the formation of lymph, which are dealt with in separate sections.

The circulating blood volume is increased in a number of states notably mental stress, muscular exercise, and high temperature. This is no doubt due in part to the constriction of the blood-depôts for there is an increase of cells as well as plasma. More rapidly moving blood also tends to sweep static corpuscles into the circulation.

A reduction of circulating blood volume is brought about by a number of conditions. It may occur in any generalised anhydræmia (i.e. loss of body water), in hæmorrhage, or if the blood pools in the capillaries as may occur when there is extensive damage to tissues. Prolonged standing has a similar effect from the pooling of blood and lymph in the legs (see "The Effect of Gravity on the Circulation"). A reduction is also produced by exposure to cold, apparently because of the vasoconstriction of the skin brought about by the nervous system, for it does not occur if the spinal cord is cut (Barbour). The skin vasoconstriction, by raising capillary

pressures, presumably increases the amount of tissue fluid and excretion by the kidney. It seems possible too, that continued mental stress may eventually reduce the blood volume and hence the effect of a holiday in causing a subject to "look better," there then being sufficient blood to fill the superficial vessels more fully. There are, however, as yet no experimental data on the subject.

Coagulation of the Blood.

Blood possesses two remarkable properties. It remains fluid in the blood-vessels throughout life, but rapidly becomes solid when shed. Both qualities are essential for the preservation of life. The maintenance of fluidity is necessary for the circulation of the blood, whilst the solidification of the shed blood provides an indispensable defence against excessive bleeding from wounds.

The coagulation of the blood is due to the formation of a jelly by the deposition of protein material called **fibrin**, and it is the formation of this body that is the fundamental change in blood clotting. When a film of almost freshly shed blood is examined under the microscope, a network of gelatinous threads or filaments of fibrin is seen, many of the threads radiating from clumps of disintegrating blood-platelets. Entangled in this mesh are both erythrocytes and leucocytes, the preponderance of the former corpuscles giving a clot of blood its characteristic red colour. The ultramicroscope reveals how the threads are built up. Minute granules first appear. These coalesce, forming needles resembling crystals which join up end to end and form the threads mentioned above. Soon, however, the whole mass contracts, its intimate structure becomes indistinguishable, and a straw-coloured liquid called **serum** is squeezed out of the clot. Blood plasma which has been deprived of leucocytes and erythrocytes clots as readily as whole blood. The presence of these corpuscles is, therefore, not necessary for blood coagulation, although their debris contains substances which may participate in clotting.

The rôle of platelets in blood clotting has been the subject of controversy. Some writers have thought that they are essential for coagulation, others have denied their importance. Recent researches indicate, however, that the platelets are normally important participants in blood clotting, but they are not always essential for that process. The removal of blood-platelets from the shed blood of fasting animals by passing it through a clay filter may completely suppress the capacity of the plasma to clot spontaneously at room temperatures, but clotting may occur after prolonged shaking or when the plasma is kept for several days at 38° C. in sterile tubes. The addition of disintegrating platelets, or extracts of them, to

deplateletised plasma rapidly produces coagulation, the speed of clotting being proportional to the amount of material added. Blood shed during the height of digestion behaves differently. It clots as rapidly as whole blood after the complete removal of the platelets.

Moreover, all the substances requisite for blood clotting can be extracted from plasma which has been deprived of all its corpuscles and platelets. It appears, then, that the plasma contains all the participants in blood clotting, but in fasting animals, and possibly when digestion is nearly inactive, the presence of platelets is necessary for a speed of coagulation sufficiently rapid for the provision of a defence against loss of blood.

Coagulation Time.—If normal blood is shed directly from a blood-vessel on to a clean watch-glass and the glass moved gently from side to side, the drop of blood ceases to move in three to ten minutes. Many mechanical devices have been invented to obtain a more accurate measurement but the practised observer usually prefers the simple method.

Bleeding Time.—The time taken for a pricked ear, dried off with blotting paper every quarter of a minute to stop bleeding, is known as the bleeding time, which is from two to four minutes. It depends not only on coagulability but the power of the injured capillary to contract.

Coagulation is inaugurated or hastened by:—

- (1) The application of warmth, *e.g.* water about 5° above body temperature. This is most important in dentistry and midwifery, and is not to be confused with the application of cold elsewhere to bring about reflex constriction of vessels.
- (2) Contact of the blood with any surface which it wets, or with tissue extracts.
- (3) Agitation or whipping, which brings such contact more rapidly into play.
- (4) The addition of **thrombase (thrombin)**, but large quantities of thrombase can be introduced slowly into the circulation without causing intravascular clotting.
- (5) The rapid intravascular injection of most tissue extracts produces clotting in the blood-vessels, but their injection slowly or in minute quantities suppresses the clotting of blood—the “negative phase” of coagulation).
- (6) Astringents, *e.g.* alum and substances like adrenaline, if applied locally, stop hæmorrhage by constricting the blood-vessels, but adrenaline also increases coagulability if injected into the blood-stream.

The coagulation of shed blood is retarded by:—

- (1) Complete contact with surfaces, *e.g.* paraffined, not wetted by blood.
- (2) Cooling the blood in a vessel surrounded by ice; the blood remains fluid for two hours or longer.
- (3) Dilution with great excess of water (20 to 40 volumes).
- (4) The addition of appropriate amounts of salts, such as sodium sulphate, magnesium sulphate, or sodium bicarbonate.
- (5) The addition of agents which precipitate the blood calcium or throw it out of action. Soluble oxalates and fluorides are too toxic to be used in living animals but are used *in vitro*. In practice a concentration of 0·6 per cent. **sodium citrate** is used. A 3·8 per cent. solution is added to 6 times its volume of blood. Citrates are extensively used for intravenous injections as in blood transfusion.
- (6) The addition of various anticoagulants, such as leech extract; various products of autolysis; a substance extracted from various tissues, especially the liver and lungs, named **heparin**, which is produced by the mast cells; and relatively large amounts of commercial peptone.
- (7) Removal of the fibrinogen by whipping it leaves defibrinated blood, which can be used for perfusing organs but is deficient in protein.
- (8) A number of anticoagulant dyes such as chlorazol fast pink are now used in experimental work (Huggett).

It is possible to carry out many experiments on blood, the result of which indicate a number of undisputed facts, although the complete explanation of the inception of the process of clotting is a subject of considerable controversy. The experimental facts are as follows:

- (1) Calcium is necessary for the clotting of blood. It may be thrown out of action by adding oxalate or citrate, but the blood will again clot if calcium is added. This discovery, by Arthus and Pagès in 1890, made possible all subsequent researches into the problem.
- (2) A precursor of fibrin (fibrinogen) exists in the circulating blood. If oxalate is added to the blood to prevent it from clotting and the blood is then centrifuged to get rid of the corpuscles, the protein fibrinogen may be precipitated by adding ammonium sulphate. It may then be redissolved in NaCl and the process repeated until the fibrinogen is pure. This fibrinogen has the unique characteristic of being coagulated by thrombase, a substance

present in the serum expressed from coagulated blood. That thrombase is not present in the circulating blood is obvious, otherwise the blood would clot in the blood-vessels.

- (3) A precursor of thrombase, prothrombase, may be isolated from oxalated plasma by precipitation with acetone. This substance, however, will not cause fibrinogen to clot in the absence of calcium or of tissue extract. These substances used to be called thrombin and prothrombin, but since they have been found to be really enzymes and ought to be called thrombase and prothrombase (Mellanby). Prothrombase can be boiled for five minutes without being destroyed. It is formed in the liver under the influence of vitamin K.
- (4) Tissue extracts, especially extracts of blood platelets, which are precipitated from ice-cold oxalated plasma by centrifuging are found to contain a substance (thrombokinase) which will not of itself clot blood, but which will in the presence of calcium activate prothrombase to do so. Howell has shown that cephalin, a phosphatide akin to lecithin, is an essential constituent of thrombokinase.

Beyond these facts we have a large amount of conflicting evidence which has led to great controversy of which the chief difficulties are:—

- (1) The nature of the factors which preserve the fluidity of the blood *in vivo*.
- (2) The mode of formation of thrombin and its manner of action on fibrinogen.

Howell believes that the mother substance of thrombin (prothrombase) exists in plasma, but is kept inactive by the anticoagulant heparin manufactured by mast cells. When blood is shed, or damaged by anything it wets, both platelets and damaged tissues liberate a compound of cephalin which neutralises the heparin and permits the activation of prothrombase by calcium-ions alone, without the intervention of any other body. Thrombase is so formed, and by union with fibrinogen forms fibrin. There is no doubt that the fluidity of normal blood is due to conditions which are unfavourable to the production of thrombase, but there are difficulties in the acceptance of Howell's teaching. For example, the intravascular injection of heparin, although it first produces incoagulable blood, is followed by an increase in the coagulability of the blood. Nevertheless heparin is used clinically. (See Jorpes, 1939.)

Pickering considered that fibrinogen and prothrombase are united with the more stable fractions of blood plasma (serum globulin and albumin) and are thus shielded from the disruptive

action of calcium-ions which is essential for the inception of blood clotting. The complex of plasma colloids possesses only a limited capacity for resistance. It breaks down immediately the blood is shed upon any surface which it wets.* As soon as the fibrinogen and prothrombase are set free the changes that result in clotting commence. Immediately afterwards blood-platelets rapidly disintegrate and, in normal wounding, tissue juices invade the stream of escaping blood. The products so liberated, with the help of calcium ions, unite with prothrombase giving thrombase, which in turn unites with fibrinogen giving fibrin. The plasma then changes from a sol to a gel, the initial steps in this change being the formation of filaments of fibrin in the manner already described. In addition, coagula closely resembling fibrin are formed by the direct union of fibrinogen and tissue juices, and it is probable that this mode of coagulation proceeds simultaneously with the clotting of fibrinogen by thrombase, although Mills maintains that this mode of clotting occurs before the formation of thrombin when blood is in contact with damaged tissues. Under artificial conditions, blood plasma can be altered from a sol to a gel by prolonged shaking without the intervention of the *debris* of platelets or tissue juices, and certain micro-organisms possess the power of clotting blood without the production of thrombase. In spite of the controversy the main facts may, however, be pieced together thus:

Prothrombase + Calcium

+ tissue juices and platelet debris (which contain thrombokinasase
chiefly cephalin)



Thrombase + Fibrinogen



Fibrin

REFERENCES.—Pickering, 1928. Howell, 1935.

The Plasma and Serum.

When shed blood is kept fluid artificially by any one of the methods mentioned on p. 316, the corpuscles gradually sink and the plasma can be removed by either a pipette or a syphon. The separation of plasma and corpuscles is more rapidly effected by using a centrifuge and the plasma volume may be determined by using a graduated tube known as the *haematocrit*.

The blood (about 5 ml.) to be studied is drawn from a vein into a dry syringe and added to a test-tube containing dried oxalate,

* If a large blood-vessel such as the aorta from a recently killed animal is cut open it may be demonstrated that its internal surface is not wetted by blood or water. This apparently depends on the lipoid character of the endothelial lining.

with which it is mixed to prevent clotting. The best method is to add the oxalated blood by means of a capillary pipette to about the 5 ml. mark on the graduated (Wintrobe) tube, and to centrifuge at 3000 revolutions per minute for half an hour. (See M.R.C. Report, *B.M.J.*, 1942, i., 209.)

The size of blood-cells is stated to increase during the day and to decrease during sleep, while changes also occur in disease. The red cells of venous blood are larger than those of arterial blood.

A relatively pure plasma may be obtained from horse's veins by what is known as the "living test-tube" experiment. If the jugular vein is ligatured in two places so as to include a quantity of blood in it, then removed and hung in a cool place, the blood does not clot for several hours. The corpuscles settle and plasma can be removed. In addition to disintegrating blood platelets, it usually contains, however, both minute clots and thrombin, and thus differs from the plasma of circulating blood. Pure and unaltered plasma has not yet been obtained outside the body, but the material available by the methods described gives a fair indication of the properties of that fluid.

Pericardial and hydrocele fluids closely resemble the plasma in composition. Usually, they contain few or no corpuscles, and are more stable than plasma. As a rule, they do not clot spontaneously, but coagulate on the addition of thrombin.

The plasma is alkaline, yellowish in tint, and its specific gravity is from 1041 to 1067, and most commonly 1050. 100 c.c. of plasma contain :—

Water	90
Solids :	
Proteins	8
Extractives (including fat)	1.4
Inorganic salts6
	} 10

Details to be memorised are given at the end of the volume.

The gases of the blood, which are normally oxygen, nitrogen, and carbon dioxide, have already been considered under Respiration.

We may now study one by one the various constituents of the plasma and serum.

A. Proteins.—Fractions of protein possessing different properties can be obtained from plasma by mixing it with different concentrations of neutral salts, those commonly used being ammonium sulphate, sodium chloride, and magnesium sulphate. They are **albumins**, **globulins**, and **fibrinogens**. The table on next page gives an approximate idea of the limits of precipitability by these salts.

It should not, however, be assumed that these fractions of protein exist in a free condition in the plasma. On the contrary, recent researches indicate that the fractions of protein obtained by the salting of plasma, particularly those called globulins, are not distinct chemical units, but parts of a larger complex that is knit together in the plasma and behaves as a coherent whole. The fractions possess, however, distinct properties (Sorensen, Pickering). For their function see p. 321.

Table illustrating the precipitability of the principal fractions of protein which are obtainable from blood plasma that has been kept fluid by the addition of sodium oxalate.

Precipitants.	Fibrinogen.	Euglobulin.	Pseudoglobulin.	Albumin.
NaCl	Precipitated at nearly half saturation.	Precipitated on saturation.
MgSO ₄	Precipitated at nearly half saturation.	Precipitated on saturation.	Precipitated on saturation.	...
(NH ₄) ₂ SO ₄	Precipitated on the addition of 15 to 27 per cent. of a saturated solution.	Precipitated on the addition of 28 to 38 per cent. of a saturated solution.	Precipitated on the addition of 36 to 44 per cent. of a saturated solution.	Precipitated on saturation.

Fibrinogen.—Fibrinogen exhibits the general characteristics of globulin with one important difference. It is clotted by thrombase and is thus distinguished from all other fractions of plasma protein. It is coagulated *in vitro* at 56° C. It is so firmly bound to prothrombase that it can be separated from that body only by coagulation of fibrinogen or by prolonged adsorption. Fibrinogen of the blood is probably combined with calcium and sodium. When freed from salts, it is incoagulable by heat (de Waele).

Fibrinogen is made by the liver under the influence of vitamin K, and apparently there is also storage there, for if blood is lost its fibrinogen content may be made up in a few hours. (Whipple, Beattie.)

Serum; is the residue of plasma left after the removal of fibrinogen as fibrin by coagulating the blood. Its proteins can be separated into serum globulin and albumin by salt precipitation; the globulin consists of euglobulin and pseudoglobulin. The albumin can also be broken into different fractions by heat coagulation. In all the vertebrates, except some fishes, *e.g.* the eel, three fractions are

obtained by heating serum to 73°, 78° and 85° C. The globulins and albumin obtained from serum exhibit the general properties mentioned on p. 280, whilst a complex of albumin and globulin possibly participates in immune reactions.

Prothrombase is probably a globulin and as already mentioned is bound to fibrinogen. When plasma clots it forms thrombase. Prothrombase also forms thrombase when whole blood or serum is treated with an excess of alcohol. The residue left after the evaporation of the alcohol is soluble in water and possesses the properties of the thrombin obtainable from blood-clots. The prolonged dialysis of prothrombase also yields thrombin.

The Functions of the Plasma Proteins.

The plasma proteins have a variety of functions.

1. They act as a medium in which the blood corpuscles are protected from damage.
2. They confer on the blood an osmotic pressure and in virtue of the size of their molecule they are not, like salts in solution, filtered off through the capillary membranes by the blood-pressure into the urine and tissue spaces.
3. The protein fibrinogen forms the fibrin of a blood clot.
4. They act as buffers and assist in preventing changes in the reaction of the blood and in carrying CO₂.
5. They probably provide the protective antibodies which protect against bacteria and their toxins. They are increased in infectious disease.
6. When exuded from the capillaries in inflammation and hæmorrhage they form a medium in which the various tissues can grow and repair themselves.

REFERENCES.—Starling 1909 ; Howe, 1925.

B. Extractives, etc.—Under this heading is a large number of substances which are very variable in amount, but which may be extracted. For the most part they are substances for which the blood is the vehicle of transport from one part of the body to another. They are non-nitrogenous and nitrogenous. The non-nitrogenous are fats, soaps, cholesterol, and sugar; the nitrogenous are urea (0·02 to 0·04 per cent.), and still smaller quantities of uric acid, creatine, creatinine, xanthine, hypoxanthine and amino-acids.

C. Salts.—There are as follows (in percentages) (E. M. Murray):—

	Plasma.	Corpuscles.	Whole Blood.
Sodium . . .	0·345	0·042	0·208
Potassium . . .	0·020	0·425	0·202
Calcium . . .	0·010	0·003	0·0·7
Magnesium . . .	0·003	0·003	0·003
Phosphorus . . .	0·003	0·003	0·003
Chloride . . .	0·380	0·185	0·292
NaCl . . .	0·625	0·374	0·481
NaHCO ₃ . . .	0·220
Traces of sulphur.			

Many of the salts of the blood are maintained at a fairly constant level of concentration; although they may vary temporarily from time to time on this constancy, which is dealt with later in a separate section, depends on the normal functioning of many organs and tissues, notably that of the heart.

The Blood-Corpuscles.

Red Corpuscles or Erythrocytes.—Human red corpuscles are circular biconcave discs with rounded edges, $\frac{1}{3000}$ inch in diameter ($8\cdot8\mu$ on the average) and about a quarter of that in thickness. When viewed singly they appear of a pale yellowish tinge; the deep red colour which they give to the blood is observable in them only when they are seen *en masse*.

Each red corpuscle is composed of a colourless envelope enclosing a semi-liquid material of which by far the most abundant constituent is hæmoglobin; the enclosing membrane is important especially in processes of osmosis such as occur when water or salt solutions are added to the corpuscles, and its presence can be clearly distinguished microscopically in the large corpuscles of amphibia. The corpuscles are perfectly elastic so that as they circulate they admit of change of form, and recover their natural shape as soon as they escape from compression.

The red corpuscles of other mammals are generally very nearly the size of human red corpuscles. They are smallest in the deer tribe and largest in the elephant. In all mammals the corpuscles are non-nucleated, and in all other vertebrates (birds, reptiles, amphibians, camels, and fishes) the corpuscles are oval, biconvex, and nucleated (fig. 130), and larger than in mammals. They are largest of all in certain amphibians (*amphiuma*, *proteus*).

Red blood-corpuscles, like all discs, tend to go into rolls or rouleaux. This is exaggerated in inflammation.

The Fragility of the Red Blood-Corpuscles.—If red blood-corpuscles are placed in distilled water they rapidly take up water by the process of osmosis, swell, burst, and discharge their hæmoglobin (*hæmolysis*). If placed in isotonic saline solution

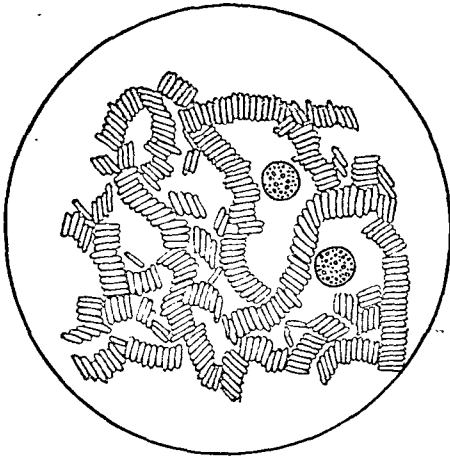


FIG. 129.—Red corpuscles in rouleaux. The white corpuscles are uncoloured.

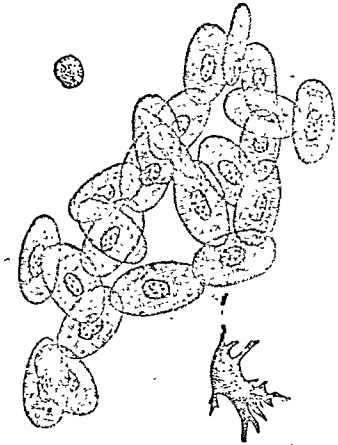


FIG. 130.—Corpuscles of the frog. The central mass consists of nucleated coloured corpuscles. The other corpuscles are two varieties of the colourless form.

they are unaffected, but the extent to which they withstand hypotonic solution varies very much especially in disease. Venous blood cells, as they contain more chloride, are more fragile than arterial cells. (See also p. 344.)

The normal fragility may be determined by exposing the cells to sodium chloride solution from 0.25 per cent. to 0.75 per cent. and counting the number of intact red cells which are present after half an hour (see below). Normal cells begin to hæmolyse at 0.48 per cent. and are completely hæmolyzed at 0.33 per cent., but in acholuric jaundice there may be hæmolysis even at 0.7 per cent. Strong salt solutions cause crenation.



FIG. 131.—Effect of hypertonic saline solution (crenation).

Dilute acetic acid causes the nucleus of the red blood-cells in the frog to become more clearly defined; if the action is prolonged, the nucleus becomes strongly granulated, and all the colouring matter seems to be concentrated in it, the surrounding cell-substance and outline of the cell becoming almost invisible; after a time the cells lose their colour altogether. A similar loss of colour occurs in the red corpuscles of human blood, which, however, from the absence of nuclei, seem to disappear entirely.

The Mean Corpuscular Movement is of importance in disease. It is the volume of the red cells in c.c. per 1000 c.c. normally

$$\frac{\text{red cell count}}{\text{about 87 cubic microns (c}\mu\text{)}}.$$

The Number of the Red Blood-Corpuscles.—The average number of red corpuscles is about 5,000,000 per cubic millimetre of blood in men and about 4,500,000 in women. These numbers, however, are subject to considerable variation. In America the number tends to be appreciably higher. An increase occurs whenever the individual is subjected to conditions of oxygen-want, such as life at a high altitude or in diseases in which the circulation is slowed. In such circumstances the bone-marrow (see below) becomes very active. A fall in the number of red corpuscles occurs when there is an abnormal destruction of corpuscles in disease or inadequate production, and temporarily after hæmorrhage.

The Hæmoglobin Content of the Blood.—From what has been said in relation to Respiration it is evident that the amount of hæmoglobin in the blood is of considerable importance. Like the number of corpuscles, it varies very much according to the efficiency of the circulation and the quality of the air breathed. In man the hæmoglobin content may be three times the usual amount if the circulation is very inefficient. The content is expressed as a percentage of an average blood which is capable of carrying 18·5 c.c. of oxygen per cent. (*i.e.* a blood which contains 14 per cent. hæmoglobin). Such a blood is said to contain "100 per cent. hæmoglobin." This estimation gives a rough idea of the oxygen-carrying power of the blood, but there is, as shown by Mc'Carthy and others, diurnal variation amounting to as much as 7 per cent. More recent and accurate determination, which, however, requires more elaborate apparatus, puts the figures at about 15 per cent. hæmoglobin and 20 c.c. of oxygen per cent. From the enumeration of corpuscles and the hæmoglobin estimation the **colour index**, or amount of hæmoglobin per corpuscle, may be determined. Thus, if there is 100 per cent. *i.e.* 5,000,000 red blood-corpuscles and 100 per cent. hæmoglobin the colour index is said to be 1; if the hæmoglobinometer gives only 50 per cent. each corpuscle contains only half the amount of hæmoglobin, *i.e.* the colour index is 0·5.

Factors affecting the Hæmoglobin Content.—These are the number of red blood-corpuscles and the amount of hæmoglobin in each. A fall in either will obviously bring about a fall of total hæmoglobin, although when there is a deficiency in corpuscle formation, as in pernicious anæmia, there may be a compensatory rise of colour index and the fall of hæmoglobin is not then so low as the corpuscle count would lead one to expect.

By far the most important cause of low hæmoglobin values is a deficiency of iron in the diet, and this is particularly liable to occur in women whose requirements are greater than those of men because of their periodic loss of blood. Small amounts of copper are also needed. The factors affecting the numbers of corpuscles are given on p. 327.

Methods.

ENUMERATION OF THE RED BLOOD-CORPUSCLES.

Several methods are employed for counting the blood-corpuscles: most of them depend upon the same principle, *i.e.*, the dilution of a minute volume of blood with a given volume of a saline solution* similar in osmotic concentration to blood-plasma, so that the size and shape of the corpuscles are altered as little as possible. A minute quantity of the well-mixed solution is then taken, examined under the microscope in a cell of known capacity, and the number of corpuscles in a given area of the cell is counted. Having ascertained the number of corpuscles in the diluted blood, it is easy to calculate the number in a given volume of normal blood.

The apparatus most frequently used at the present time is known as the Thoma-Zeiss hæmacytometer. It consists of a carefully graduated pipette, in which the dilution of the blood is made; this is so formed that the capillary stem has a capacity equalling one-hundredth of the bulb above it. If the blood is drawn up in the capillary tube to the line marked 0.5 (fig. 132) the saline solution may afterwards be drawn up the stem to the line 101. This gives a dilution of 1-200 as the last 1 does not mix. The blood and the saline solution are well mixed by shaking the pipette. The other part of the instrument consists of a glass slide (fig. 133) upon which is mounted a covered disc, *m*, accurately ruled so as to present one square millimetre divided into 400 squares of one-twentieth of a millimetre each. The micrometer thus

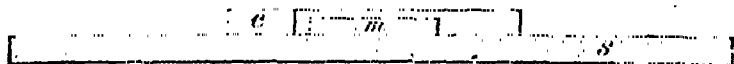


FIG. 133.

made is surrounded by another annular cell, *c*, which has such a height as to make the cell project exactly one-tenth millimetre beyond *m*. If a drop of the diluted blood is placed upon *m*, and *c* is covered with a perfectly flat cover-glass, the volume of the diluted blood above each of the squares of the micrometer, *i.e.* above each $\frac{1}{100}$, will be $\frac{1}{1000}$ of a cubic millimetre. Five large squares (*i.e.* 5×16 small) are counted and the average per small square taken by dividing by 80. This number multiplied by 4000 and again by 200 to allow for the dilution gives the number of corpuscles in a cubic millimetre of undiluted blood, *i.e.*

where x = the number in five large squares, $\frac{x}{80} \times \frac{4000 \times 200}{1}$.

In actual practice it will be noticed that no arithmetic is necessary, 0000 simply being added to the number found in the five large squares.

ENUMERATION OF THE WHITE BLOOD-CORPUSCLES.

The enumeration of the colourless corpuscles depends on the same principle, but the counting has to be carried out over the whole square millimetre. The blood is diluted (1-20) in a similar special pipette with dilute acetic acid to hæmolyse the red blood-corpuscles and a stain is usually added. Since the dilution is 1-20 and the cubic capacity of the area counted $\frac{1}{10}$ of a cubic millimetre, multiplication of the number counted by 200 gives the number of white corpuscles in the whole cubic millimetre.

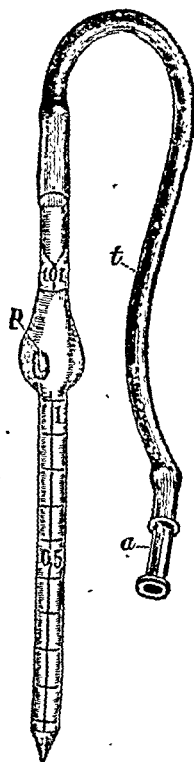


FIG. 132.—The pipette of a Thoma-Zeiss hæmacytometer for red blood-corpuscles.

* Hayem's solution has HgCl_2 as an antiseptic and Na_2SO_4 .

Differential Count.—The differentiation of the varieties of colourless corpuscles (which is most important from the standpoint of disease) can be accomplished after the appropriate staining of blood-films. Five hundred white blood-corpuscles are counted and the percentage of each variety calculated.

ESTIMATION OF HÆMOGLOBIN.

One type of hæmoglobinometer, that of Haldane, consists of two tubes, one of which contains 20 cub. mm. of standard blood (see below) laked and diluted to 100. A little distilled water is placed in the other tube, which is graduated, and 20 cub. mm. of the blood (measured in a pipette) being estimated is added.

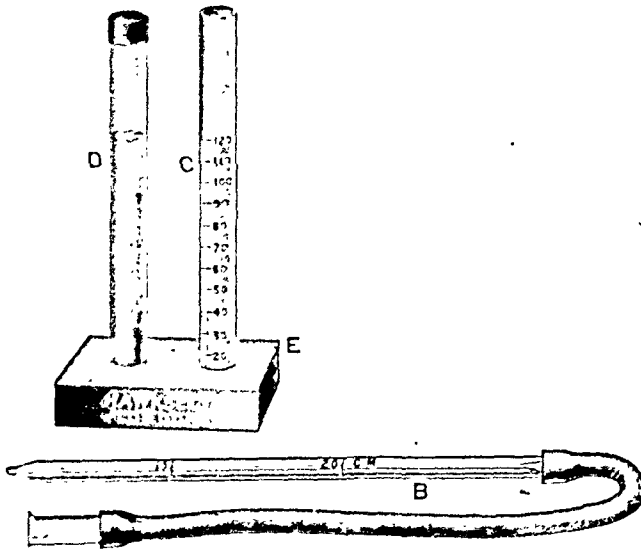


FIG. 134.—The Gowers-Haldane Hæmoglobinometer.

This is diluted with distilled water * till the colours are alike and the dilution is read off. If, for example, the colours are alike when the dilution has only been 50 (instead of the normal 100), the blood contains only 50 per cent. of the normal hæmoglobin. Commonly, the standard used is a carmine jelly of the same tint as normal blood (Gowers), but since this is liable to fade, normal blood the hæmoglobin of which is converted into carboxy-hæmoglobin is used (Haldane), but in this instance carbon monoxide (coal-gas) must be mixed with the diluted blood under investigation. The blood used in the Haldane standard is capable of carrying 18.5 per cent. c.c. of oxygen per 100 c.c. of blood.

Hæmoglobin Standards.—In all researches attention to details given in a special report of the Medical Research Council, 1912, *B.M.J.*, p. 239, and the use of a properly standardised hæmoglobinometer is most essential.

The colour of the standard should be checked against blood capable of carrying 18.5 c.c. per cent. of oxygen or containing 14 mg. of hæmoglobin per 100 c.c. of blood.

The Origin of the Red Blood-Corpuscles.—Surrounding the early embryo is a circular area, called the vascular area, in which the first rudiments of the blood-vessels and blood-corpuscles are developed. Here the nucleated embryonic cells of the mesoderm, from which

* The addition of a very minute quantity of NH_4OH keeps the hæmoglobin in solution and is better (Haldane).

the blood-vessels and corpuscles are to be formed, send out processes in various directions, and these, joining together, form an irregular meshwork. From some of these endothelial cells the first red blood-corpuscles, known as *megaloblasts*, are developed but they are nucleated and larger than adult corpuscles. Next appear the *erythroblasts* which have nuclei with fine chromatin network, and later the *normoblasts* in whose deeply staining (with basic dyes) nuclei the network is now absent. Non-nucleated cells now appear and as their cytoplasm has a network which stains with cresyl blue they are known as *reticulocytes*. These cells give way to the adult cells but readily appear again if there is any severe call on the blood-producing areas. Hæmoglobin is added at the erythroblast stage. In severe cases nucleated cells may also reappear. See Summary on p. 334. References—Sabin, 1928; Rous, 1933.

In the *fœtus* the liver and spleen take part in blood formation, but in the adult it is confined to the red bone-marrow. The long bones do not, however, take part normally except in early life, but in an emergency the yellow marrow rapidly becomes vascularised and takes on the function of blood formation.

It has now been clearly shown that the stomach and liver are concerned in blood production in another way. It was found by Whipple that dogs would recover from being bled more rapidly than normally if fed on liver.

Castle has shown that Brunner's glands and corresponding ones in the pylorus produce an "intrinsic factor" which is somewhat like an enzyme. It acts upon an "extrinsic factor" in the food which forms a substance necessary for blood production. This substance is stored in the liver. When the stomach factor or the pyloric region is removed megaloblasts fail to mature.

The factors affecting the number of red blood-corpuscles are of considerable practical importance in relation to anæmia. They are:—

- (1) Hæmopoietic factors, extrinsic and intrinsic, which are affected by the state of the stomach and liver.
- (2) Vitamin C in the diet.
- (3) Thyroxine from the thyroid gland.
- (4) Iron and copper for the hæmoglobin.
- (5) The state of the bone marrow.
- (6) The speed of destruction of the cells.
- (7) The presence of chronic sources of blood loss, notably excessive menstruation in women, ulcers of the alimentary canal, or bleeding hæmorrhoids (piles).

Lack of 1-6 of these factors leads to different varieties of anæmia or blood deficiency. The possible sources of iron in nature are discussed in a later section on Diet. The successful treatment

of pernicious anæmia, for long a fatal disease,* with liver and its extracts and later with extracts of stomach, is a tribute to the value of experimental physiology in the alleviation of suffering.

The Fate of the Red Blood-Corpuscles.—The fact that the pigments of bile and of blood are chemically related has long suggested that the former are derived from the latter, and other evidence has indicated that the red blood-corpuscles have, like all other cells of the body, a tolerably definite term of existence, estimated at about three to four months,† after which they die and are replaced. This is suggested by the fact that blood is constantly being formed, and red cells in the process of breaking down have been observed in organs such as the spleen. The evidence appears to indicate that the breakdown of the corpuscles occurs for the most part as a simple mechanical result of wear and tear (Rous) and we know that such *fragmentation* is very liable to take place in artificial perfusions with pumps. Some idea of the duration of the life of the corpuscle can be obtained by calculating the number of blood-corpuscles which would be sufficient to supply pigment for the amount of bile secreted daily. This view is supported by the fact that stored blood loses a number of its qualities after about a month. Its corpuscles begin to disintegrate and the plasma develops a toxic substance with a peptone-like and choline-like action (Gilding). In diseases involving blood destruction the presence of the iron-containing pigment hæmosiderin which accumulates in the liver and spleen is readily demonstrable by the Prussian blue reaction.

The broken-down red blood-corpuscles are taken up by the *reticulo-endothelial system* which, as we shall see, separates and sets free into the blood-stream the pigment and the iron. (See Rous, 1923.)

Reticulo-Endothelial System (Aschoff) consists of cells scattered widely in different regions. Some of the cells are wandering cells, such as the *clasmatoocytes* of the connective tissue and the mononuclear cells of the blood and spleen; others are sessile, for example the stellate cells of Kupffer, which constitute an imperfect lining for the hepatic capillaries. Other sessile components of the reticulo-endothelial system are the endothelium of the lymph sinuses and splenic sinuses and that of the capillaries of the bone-marrow and suprarenal glands, and the branched reticulum cells of the bone-marrow, lymphoid tissue, spleen and thymus. Reticulo-endothelial cells possess in common the property of ingesting particles such as cell-debris and bacteria; for this reason they are called *macrophages* (in contrast to the *microphages* or polymorphonuclear leucocytes). In addition, they have the closely related power of taking up

* Pernicious anæmia is brought about by chronic inflammation of the stomach.

† The older view was only thirty days.

foreign colloids, such as Indian ink. An important function attributed to these cells is the formation of bilirubin from hæmoglobin. (See Sacks, 1926.)

Why or how the red cells break down is not yet known, but once they are broken down, the free blood pigment is converted into bile pigment by the Kupffer cells. This is shown by the fact that if blood pigment is injected into the circulation or if hæmolysis of the red cells is caused by arseniuretted hydrogen bile pigment appears in the blood, but not so if the reticulo-endothelial system has been thrown out of action by previously making it take up other foreign matter such as a colloidal substance or by removing the majority of the Kupffer cells in animals where they are chiefly situated in one organ, *e.g.* the liver of the bird.

It is not to be imagined that blood destruction and bile formation occur only in certain organs. They probably occur in all organs, and in the colour of an ordinary bruise we have in reality the formation of bile pigment locally. We shall trace this pigment further in relation to the bile.

The simplest method of demonstrating the activity of the reticulo-endothelial system is that of Gilding. A white rabbit is injected with Indian ink. Almost immediately its skin, ears and mucous membranes are black. After about ten minutes the blackness disappears and when a post-mortem is now made the liver, spleen and bone marrow will be seen to have become black. Histological sections show the accumulation of the ink in the reticulo-endothelial cells.

The White Blood-Corpuscles.—These corpuscles are masses of nucleated protoplasm; they are nearly spherical when at rest, but owing to their amoeboid movements (see p. 7) exhibit considerable changes in outline when they are active, as they are at body temperature. They are also known as **leucocytes**. (See Bunting, 1922)

The number of white blood-corpuscles varies at different times of the day (Bernard Shaw). In the morning or after a rest in the horizontal position they are about 6000 per cub. mm. but increase after midday. They are increased by activity, by a meal, after the injection of adrenaline, and in asphyxia; indeed, the determining of the rise in the numbers of white blood-corpuscles during rebreathing from a simple rubber bag might be used as a test of the availability of such cells (McDowall). They may be enormously increased in most infections (*e.g.* 60,000 in pneumonia). If, indeed, they do not so increase, the forecast for the recovery of the patient is not good. In a few infections they are decreased (*e.g.* influenza). (See Garney and Bryan, 1935.)

Several varieties of colourless corpuscles are found in human blood. (See coloured plate facing p. 334.)

They are of two main groups, agranulocytes, *i.e.* without granules, and granulocytes, those with granules in their cytoplasm.

Agranulocytes—(a) *Lymphocytes*.—These are only a little larger than red corpuscles. The nucleus is relatively large; and usually round; the protoplasm around it forms quite a narrow zone. The nucleus, as is the case with all nuclei, is basophile, and stains with such basic dyes as methylene blue. The protoplasm presents no distinct granules and is also basophile. The lymphocytes comprise about 25-40 per cent. of the total colourless corpuscles. This variety of corpuscle is much increased in *chronic* infections, *e.g.* tuberculosis.

(b) *Large mononuclears, Monocytes*.—A relatively small oval nucleus lies near the centre of basophile protoplasm, which again presents no definite granulation. Their diameter is 12-20 μ , and they form only 1 per cent. of the total colourless corpuscles. This variety is commonly increased in protozoal infections, *e.g.* malaria.

(c) *Transitional leucocytes*.—The cell-body is somewhat smaller and is mainly basophile. A certain amount of neutrophile granulation may be seen. The nucleus may present all gradations between an oval and lobed condition. They are very rare (about 2 per cent.). They were called transitional on the doubtful hypothesis that they represent an intermediate condition between the large mononuclear leucocytes and the polymorphonuclear leucocytes described below.

Granulocytes.—These are all really polymorphonuclear, but the latter term is by convention confined to the neutrophils.

(1) *Polymorphs*.—These are 9-12 μ in diameter, and form the main mass of the colourless corpuscles (55-70 per cent.). They have several nuclei, which are strongly basophile and present many different shapes, and are usually connected by threads of chromatin. The protoplasm is finely granular, and stains with neutral, and faintly with acid aniline dyes (such as eosin). In certain pathological conditions—for instance, in diabetes mellitus—the cell-protoplasm contains excess of glycogen. The polymorphs are greatly increased in most *acute* infections.

(2) *Eosinophils*.—These are usually larger than the preceding (12-15 μ in diameter). They contain either a single irregular-shaped nucleus, or more often two or three nuclei of unequal size. Their protoplasm contains large distinct granules which have an intense affinity for acid dyes such as eosin, and are therefore termed oxyphile, acidophile, or eosinophile. They are stated to be less actively amœboid than the polymorphonuclear leucocytes. They comprise from 2 to 4 per cent. of the total colourless corpuscles. They are increased in anaphylactic states produced by the injection of foreign protein, in asthma, and especially in infestation with animal parasites, but the reason for these increases is unknown.

(3) *Basophils*.—These cells are present in connective tissues

generally, but they are very rare in normal blood. Less than 0.5 per cent. is usually present. They measure about $10\ \mu$ across; their nucleus is single and irregular in shape. The granules in the protoplasm are much more basophile than the nucleus.

Phagocytosis.—The most important outcome of the amœboid movement of the colourless corpuscles is their power of ingesting foreign particles, such as bacteria, which they engulf and digest

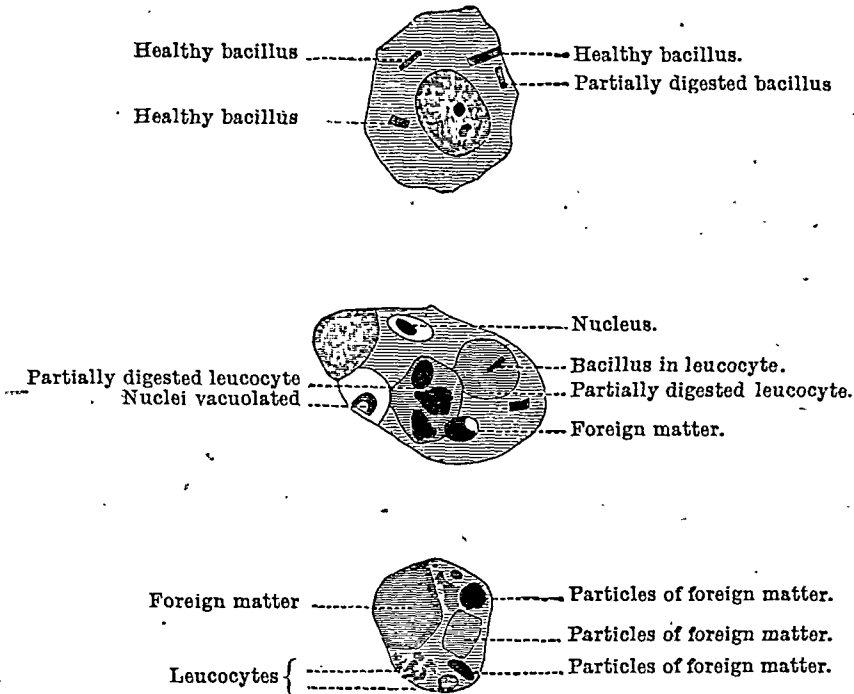


FIG. 185.—Phagocytes containing bacilli and other structures undergoing digestion. (Ruffer.)

This is called phagocytosis. The polymorphonuclear leucocytes, which are the most active phagocytes, contain a trypsin-like enzyme which digests protein in a neutral or faintly acid medium. If it diffuses out in small quantities it is destroyed by an anti-enzyme in the plasma but in large quantities it digests tissues to form pus. (See Mudd, M'Cutcheon, and Lucké, 1934.)

The Blood-Platelets.—Besides the two principal varieties of blood-corpuscles, a third kind has been described under the name blood-platelets. These are colourless disc-shaped or irregular bodies, much smaller than red corpuscles. Different views are held about their origin. There is, however, no doubt that they do occur in living blood, and are possibly shed off from cells such as the megakaryocytes (giant-cells) of the marrow and spleen. They show no amœboid movements. Their importance in relation to the

coagulation of the blood has already been pointed out. The normal number of platelets per cubic millimetre varies but averages about 250,000.

Origin of the White Blood-Corpuscles (in the Adult).—The *lymphocytes* are formed in lymphoid tissue wherever this is found (lymphatic glands, tonsils, etc.); the lymph leaving a lymphoid structure is thus found to be richer in lymphocytes than that entering the structure. The lymphocytes enter the blood-stream by the thoracic duct and the right lymphatic duct. In the cortical follicles of lymphatic glands, the clearer central portion called the "germ-centre," where active karyokinesis occurs, is thought to be the actual seat of formation of lymphocytes. The large lymphocytes of the blood resemble the cells of the germ-centres.

The *polymorphonuclear leucocytes* are developed in the red marrow of the bones from the *myelocytes*. The latter are rounded cells the cytoplasm of which contains neutrophile granules; their nuclei are rounded and but poorly marked off from the cytoplasm. The myelocytes are the most abundant cellular constituent of the bone-marrow. In various infective diseases, *e.g.* pneumonia, there is a great increase of leucocytes in the blood (leucocytosis); this is associated with proliferation of the myelocytes in the marrow and some may be swept out in the immature state into the blood-stream. Certain of the myelocytes contain coarse granules; in some the granules are eosinophile and such *eosinophile myelocytes* are the precursors of the *eosinophile leucocytes*; whilst in others basophile granules are present and these *basophile myelocytes* give rise to the *basophile cells* of the blood.

The origin of the *large mononuclear leucocyte* is involved in the mists of controversy. According to one view it arises from the cells of the reticulo-endothelial system (see p. 361); in favour of this hypothesis is the fact that in an animal injected with a foreign colloid, such as colloidal silica, the cells of this system, *e.g.* the Kupffer cells of the liver capillaries, seize on the colloid with avidity, swell up and divide, one product of division passing into the blood-stream as a cell resembling a mononuclear leucocyte. According to another view, however, this class of leucocyte is developed from the myelocyte. The *transition forms* are probably to be regarded as related to the large mononuclears; it is no longer believed that they represent an intermediate stage between these and polymorphonuclears. (See Summary on p. 334.)

In determining whether leucocytes have arisen from myelocytes or from other cells, use has been made of the peroxidase reaction. Marrow cells are believed to contain peroxidases, so that when they are acted on by a mixture of benzidine and hydrogen peroxide, blue granules become visible in their cytoplasm. Such granules can be

demonstrated in polymorphonuclears and eosinophiles, but not in lymphocytes and slightly in large mononuclear cells. The basophiles, although undoubtedly of marrow-origin, fail to show blue granules in their cytoplasm.

The Movements of the White Blood-Corpuscles.—If a small blood-vessel slightly larger than a capillary is observed under the microscope, say in the web of the frog's foot, white blood-corpuscles may be seen lolling along the wall of the vessels. There seems little doubt that they can pass through the walls of the capillary, and have a remarkable power of accumulating at a point of injury or bacterial invasion. If a section is cut across a small boil a region thickly packed with white blood-corpuscles is seen surrounding the infected region and shutting it off from the rest of the body. We have already noted that white cells and phagocytic cells are very alike, if not identical with those found in areolar tissue.

Leucocytes if placed on a warm stage may be seen to make **amœboid movements**. They change their shape by throwing out processes known as pseudopodia like those of an amœba. First one and then another of these processes is thrown out and this is followed by a movement of the cell body as a whole. The exact cause of the movement is quite unknown, but there seems little doubt that its direction is affected by chemiotactic influences.

Chemistry of the Blood-Corpuscles.

The White Blood-Corpuscles.—Their nucleus consists of nuclein, their cell protoplasm yields proteins belonging to the globulin and nucleo-protein groups. The protoplasm of these cells often contains small quantities of fat and glycogen.

The Red Blood-Corpuscles.—1000 parts of red corpuscles contain—

Water	688	parts.
Solids {	Organic	303.88	„
	Inorganic	8.12	„

One hundred parts of the dry organic matter contain—

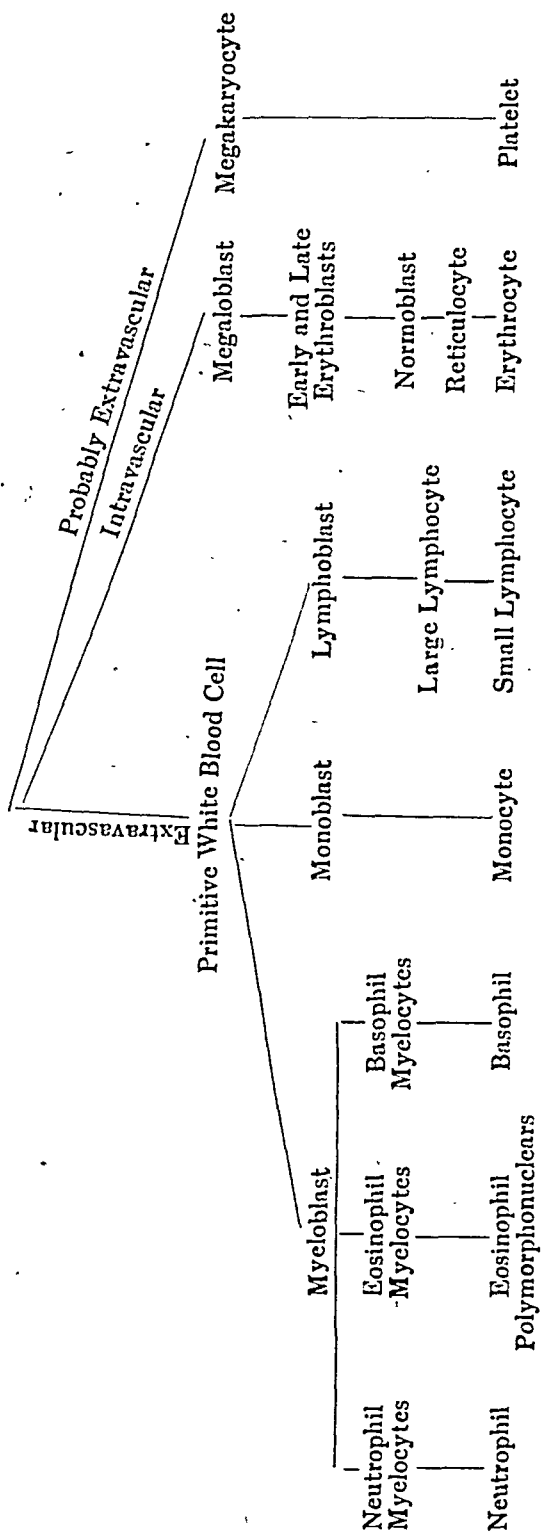
Protein (excluding hæmoglobin)	5 to 12	parts.
Hæmoglobin	36 to 94	„
Phosphatides calculated as lecithin	1.8	„
Cholesterol	0.1	„

The protein present appears to be similar to the nucleo-protein of white corpuscles. The mineral matter consists chiefly of chlorides of potassium and sodium, and phosphates of calcium and magnesium. In man and most other animals potassium chloride is more abundant than sodium chloride.

SUMMARY OF

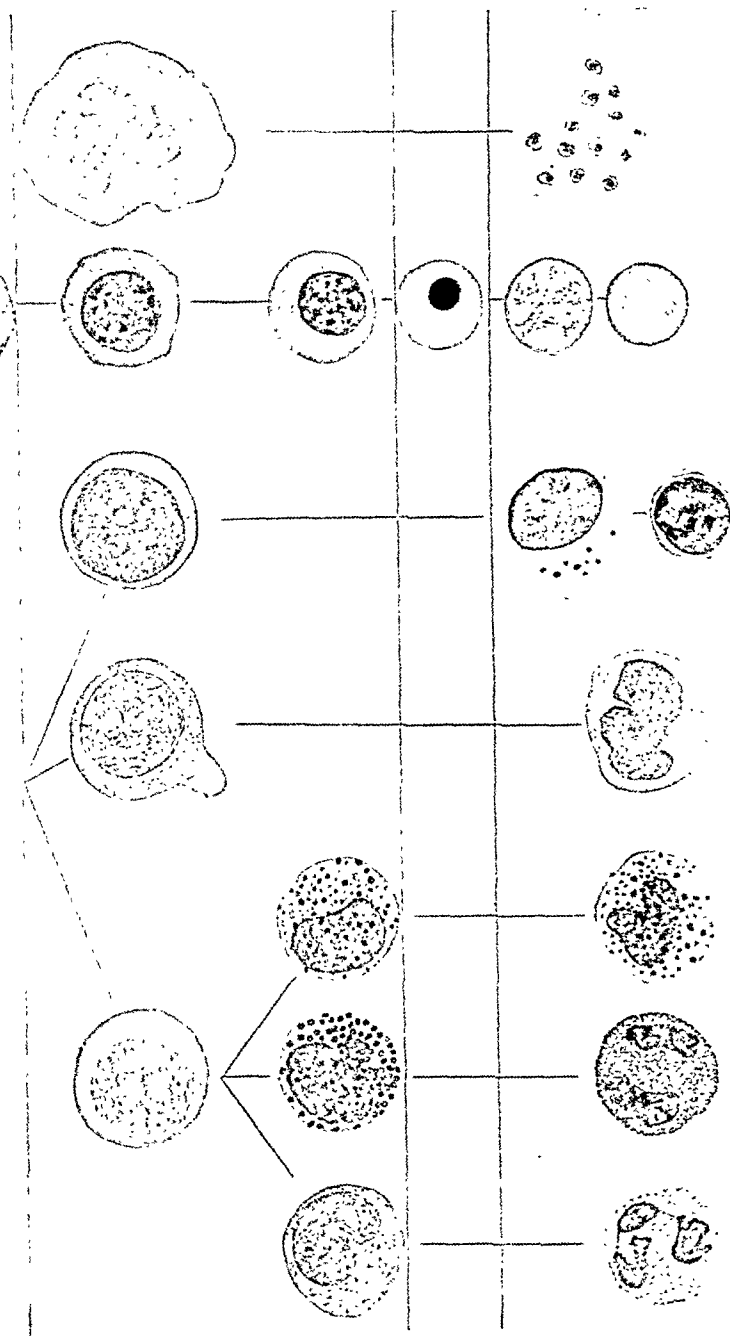
ORIGIN OF BLOOD CELLS

Reticulo-endothelial System (in bone marrow, spleen, lymph glands)



RETICULO-ENDOTHELIAL SYSTEM

PRIMITIVE WHITE BLOOD CELL



The development of the cells of the blood (see p. 334).

By permission from Whitby and Britton's *Disorders of the Blood*. (Churchill.)

The Blood Pigments or Hæmochromes.

In both the plant and animal worlds pigments play an important part in the supply of oxygen.

Hæmoglobin and Oxyhæmoglobin.—Pigments are by far the most abundant and important of the constituents of the red corpuscles. These are conjugated proteins, a compound of the protein globin with the complex iron-containing pigment **hæm**, which belongs to the class of pigments known as **porphyrins** which contains also the green pigment of plants—chlorophyll—and cytochrome, the pigment which is associated with oxidations in cells. These pigments, together with the bile pigments and other animal pigments which are derived from them, are sometimes known as the **Pyrrole Pigments**, as they are derived chemically from the simple hetero-ring compound pyrrole, C_4H_4N (see formula below). Some respiratory pigments, such as the green chlorocruorin of certain worms, contain iron, but the hæmocyanin of molluscs and crustacea contains copper. In the invertebrate animals the hæmoglobin is not in the corpuscles but free in the plasma.

Hæmoglobin is the pigment which gives the red colour to the blood. When combined with oxygen (but not oxidised) it becomes the familiar bright red oxyhæmoglobin which has already been studied in relation to Respiration. The actual shade of red which blood assumes depends on the proportion of hæmoglobin to oxyhæmoglobin, and, as we have seen, even venous blood contains a considerable amount of the latter.

Crystals of oxyhæmoglobin may be obtained with readiness from the blood of such animals as the rat, guinea-pig, or dog; with difficulty from other animals, such as man, ape, and most of the common mammals. The following methods are the best:—

1. Mix a drop of defibrinated blood of the rat on a slide with a drop of water or Canada balsam; put on a cover-glass; in a few minutes the corpuscles are rendered colourless, and then the oxyhæmoglobin crystallises out from the solution so formed.

2. On a larger scale, crystals may be obtained by mixing the blood with one-sixteenth of its volume of ether; the corpuscles

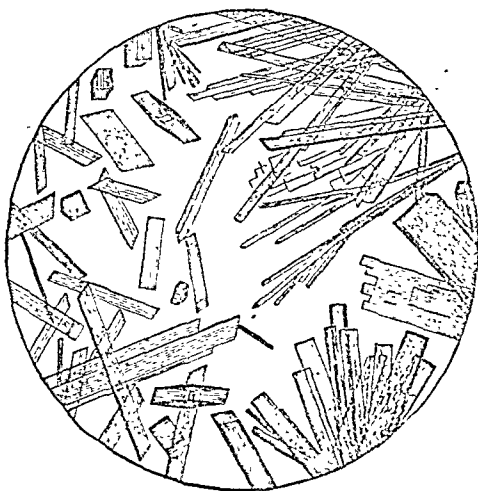


FIG. 136.—Crystals of oxyhæmoglobin—prismatic, from human blood.

dissolve, and the blood assumes a *laky* appearance. After a period varying from a few minutes to days, abundant crystals are deposited.

The shape of the oxyhæmoglobin crystals in different animals varies somewhat, probably owing to the varying amounts of water of crystallisation they contain.

Hæm, the parent pigment chemically, is chiefly of academic interest but has the property of being very easily oxidised or reduced. It exists in both forms (see schema). The term hæm usually refers to reduced hæm. In nature, however, it does not seem likely that it ever occurs free from globin. The globin prevents the oxidation of the hæm without interfering with its power to carry oxygen in loose combination. If the globin is thrown out of action in blood the hæm becomes oxidised and methæmoglobin is formed (see below). This occurs to hæmoglobin crystals if they are stored.

Hæmatin.—On adding an acid or alkali to hæmoglobin, it is broken up into two parts—a brown pigment called *hæmatin*, which contains all the iron of the original substance, and *globin*.

Hæmoglobin disintegrating in the circulation is first split into globin and reduced hæmatin (ferrous) and is immediately oxidised to hæmatin (ferric) which in man combines with serum albumin to form methæmalbumin.

Hæmatin has the formula $C_{34}H_{33 \text{ or } 35}O_5N_4Fe$. It presents different spectroscopic appearances in acid and alkaline solutions (see accompanying plate). It may be reduced in alkaline solution by adding a reducing agent, and the well-marked absorption spectrum of reduced hæmatin or **hæmochromogen** forms the most delicate of the spectroscopic tests for blood pigment. Hæmochromogen is of a red colour; hæmatin is brownish.

Hæmochromogen in neutral solution undergoes spontaneous oxidation to the ferric state of parahæmatin. It was this fact that suggested that the function of the natural globin in hæmoglobin is to prevent this oxidation. The reducing agent destroys this protective action of the globin by denaturing it.

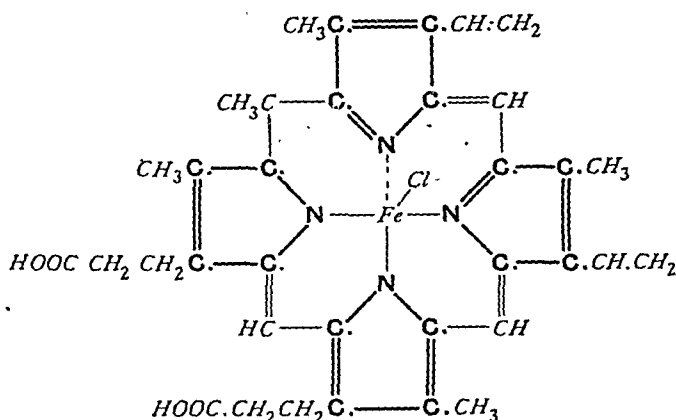
Hæmin is of great importance, as the obtaining of this substance forms the best chemical test for blood. The test is much used in medico-legal work. Hæmin crystals may be prepared for microscopical examination by boiling a fragment of dried blood with a drop of glacial acetic acid on a slide; on cooling, triclinic plates and prisms of a dark brown colour, often in star-shaped clusters and with rounded angles (fig. 137), separate out. In the case of an old blood-stain it is necessary to add a crystal of sodium chloride. Fresh blood contains sufficient sodium chloride in itself.

The action of the acetic acid is to split the hæmoglobin into hæmatin and globin; a hydroxyl group of the hæmatin is then replaced by chlorine.

The structure of hæmin has now been confirmed by synthesis and has been shown to consist of four pyrrole rings (dark in figure) linked together. The various hæm differ in having different side-chains, *e.g.* while in the case of the bile pigments the iron is removed while the large ring breaks up to form a chain.

From hæmin it is possible to produce the parent pigment hæm (see schema below).

Hæmatoporphyrin, $C_{34}H_{38}O_4N_6$, is iron-free hæmatin; it may



A suggested formula of hæmin (not to be memorised).

be prepared by mixing blood with strong sulphuric acid; the iron is taken out as ferrous sulphate. It is also found sometimes in nature; it occurs in certain invertebrate pigments, and may also be found in

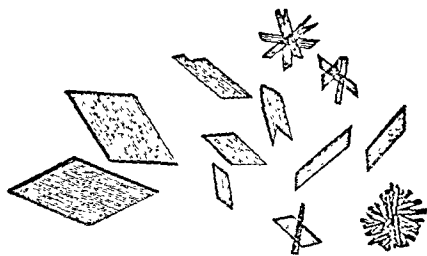


FIG. 137.—Hæmin crystals. (Frey.)

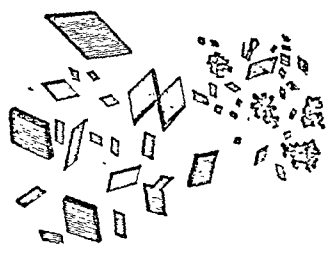


FIG. 138.—Hæmatoidin crystals. (Frey.)

certain forms of pathological urine. Even normal urine contains traces of it. It is isomeric with the bilirubin of bile. It presents different spectroscopic appearances according as it is dissolved in acid or alkaline media. The absorption spectrum figure (No. 9) is that of acid hæmatoporphyrin.

Hæmopyrrol is formed by reduction from hæmatoporphyrin and proves to be a mixture of several pyrrol derivatives. Similar derivatives are obtained from chlorophyll, a fact which illustrates the near relationship of the principal animal and vegetable pigments.

The relationships of the derivatives of blood pigment are shown in the following scheme in which those which the student usually prepares are given in dark letters. In more accurate work the starting point is usually hæmin crystals prepared from blood.

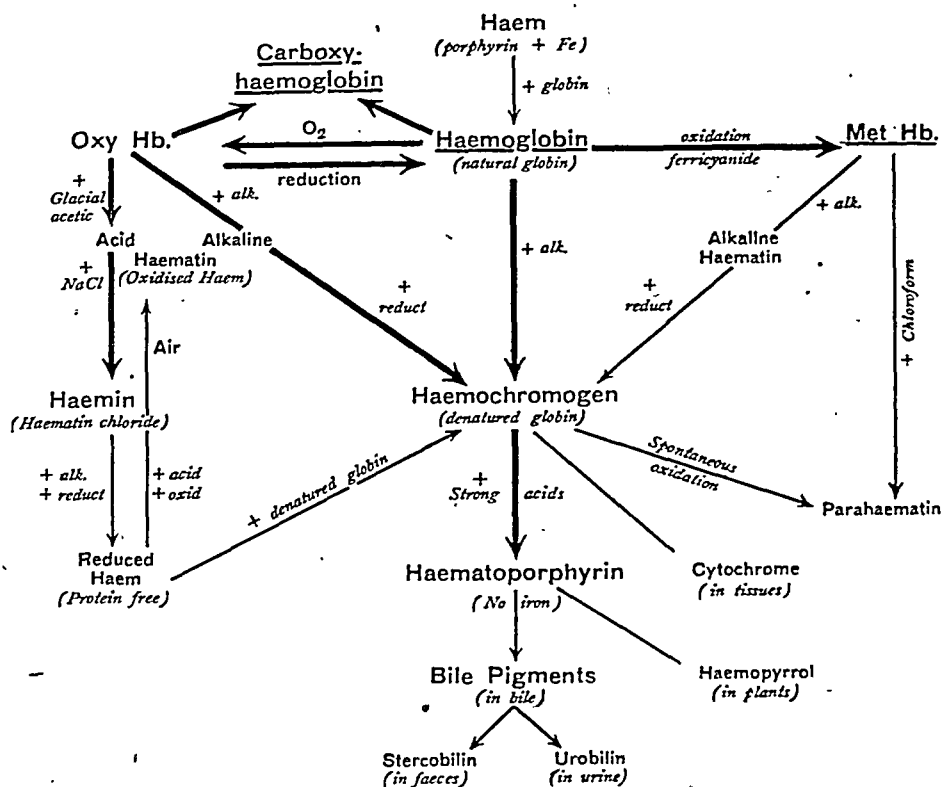


FIG. 189.—Derivatives of hæm related to hæmoglobin. Students are commonly expected to prepare and recognise the substances in large print. Hæm is reduced hæm and hæmoglobin is sometimes called reduced hæmoglobin.

Hæmatoidin.—This substance is found in the form of yellowish red crystals (fig. 138) in old blood extravasations, and is derived from the hæmoglobin. Its crystalline form and the reaction it gives with fuming nitric acid show it to be closely allied to *bilirubin*, the chief colouring matter of the bile, and on analysis it is found to be identical with it. (See Bile.)

Hæmatoidin, like hæmatoporphyrin, is free from iron, but differs from it in showing no absorption bands in the spectrum.

Compounds of Hæmoglobin.

Hæmoglobin forms at least four compounds with gases:—

With oxygen	{ 1. Oxyhæmoglobin.
With carbon monoxide	{ 2. Methæmoglobin.
With nitric oxide	3. Carbon monoxide hæmoglobin.
	4. Nitric oxide hæmoglobin.

These compounds have similar crystalline forms with the exception of methæmoglobin; each consists of a molecule of hæmoglobin combined with one molecule of the gas in question. They part with the combined gas somewhat readily; they are arranged in order of stability in the above list, the least stable first.

Oxyhæmoglobin is the compound that exists in arterial blood. Many of its properties have already been described in relation to Respiration.

We have seen that the oxygen may be removed by exposing the blood to a vacuum. The blood may also be reduced by passing hydrogen through it or by addition of other reducing agents, such as ammonium sulphide or Stokes' reagent (an ammoniacal solution of ferrous tartrate), or, best of all, sodium hydrosulphite. One gramme of hæmoglobin will combine with 1.34 c.c. of oxygen.

If any of these methods for reducing oxyhæmoglobin is used, the bright red (arterial) colour of oxyhæmoglobin changes to the darker (venous) tint of hæmoglobin. On once more allowing oxygen to come into contact with the hæmoglobin, as by shaking the solution with the air, the bright arterial colour returns.

These colour-changes may be more accurately studied with the spectroscope, and the constant position of the absorption bands seen constitutes an important test for blood pigment. It will be first necessary to describe briefly the instrument used.

The Spectroscope.—When a ray of white light is passed through a prism, it is refracted or bent at each surface of the prism; the whole ray is, however, not equally bent, but it is split into its constituent colours, which may be allowed to fall on a screen. The band of colours beginning with the red, passing through orange, yellow, green, blue, and ending with violet, is called a *spectrum*: this is seen in nature in the rainbow.

The spectrum of sunlight is interrupted by numerous dark lines crossing it vertically, called Fraunhofer's lines. These are perfectly constant in position and serve as landmarks in the spectrum. The more prominent are A, B, and C, in the red; D, in the yellow; E, b, and F, in the green; G and H, in the violet. These lines are due to certain volatile substances in the solar atmosphere. If the light from burning sodium or its compounds is examined spectroscopically, it will be found to give a bright yellow line, or, rather, two bright

yellow lines very close together. Potassium gives two bright red lines and one violet line; and the other elements, when incandescent, give characteristic lines, but none so simple as sodium.

A convenient form of small spectroscope is the *direct vision spectroscope*, in which, by an arrangement of alternating prisms of crown and flint glass, the spectrum is observed by the eye in the same line as the tube furnished with the slit—indeed, slit and prisms are both contained in the same tube.

If we interpose between the source of light and the slit a piece of coloured glass, or a solution of a coloured substance contained in a vessel with parallel sides, the spectrum is found to be no longer continuous, but is interrupted by a number of dark shadows, or *absorption bands* corresponding to the light absorbed by the coloured medium. Thus a solution of oxyhæmoglobin of a certain strength gives two bands between the D and E lines; reduced hæmoglobin gives only one; and other red solutions, though to the naked eye similar to oxyhæmoglobin, will give characteristic bands in other positions.

The Properties of Hæmoglobin.

We have seen already the importance of hæmoglobin in relation to respiration. We may now summarise its properties and it will be seen how well it is adapted to perform its functions.

It has a peculiar affinity for oxygen, as shown by its dissociation curve, and just as readily gives it up.

It is amphoteric, that is, it unites with acids and alkalies. When oxidised, *i.e.* oxyhæmoglobin, in the red blood-corpuscles its reaction is 7·4, and it acts as an acid and combines with base.

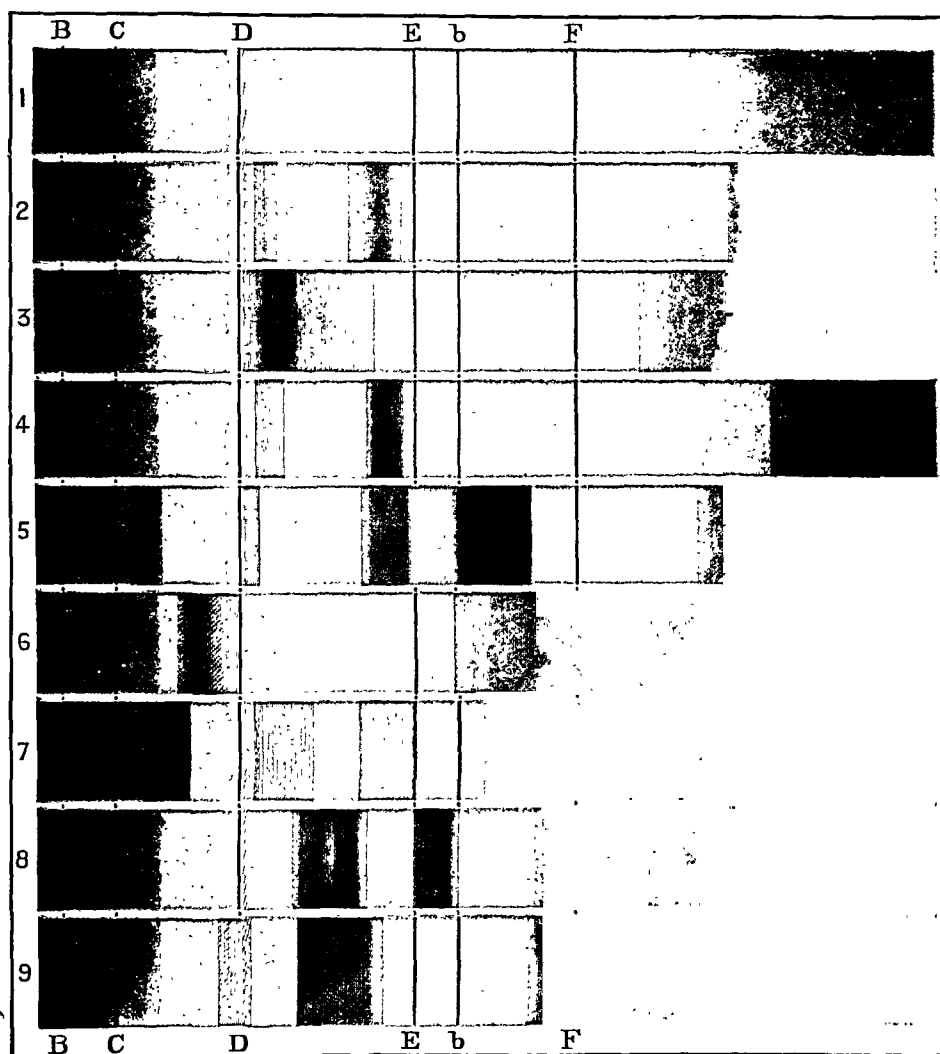
It takes up acids especially when reduced. This property, as we have seen, plays an important part in the carriage of carbon dioxide, but also is important in the maintenance of the reaction of the body generally.

It is a precursor of the bile pigment.

Methæmoglobin.—As has been said, the globin prevents the oxidation of hæm by the oxygen of the air, but this occurs if the globin is thrown out of action by adding a variety of agents especially protein precipitants or oxidising agents. Methæmoglobin, a very dark brown pigment, is thus formed. It is commonly produced by adding potassium ferricyanide or amyl nitrite to blood, and as it also may occur in certain diseased conditions and pass into the urine, it is of considerable practical importance.

Potassium ferricyanide produces another effect as well, namely, it causes an evolution of oxygen, if the blood has been previously laked. In relation to respiration we have already seen that use is

BLOOD-SPECTRA COMPARED WITH SOLAR SPECTRUM.



1. Solar spectrum.
2. Spectrum of dilute solution of oxyhæmoglobin.
3. " " reduced hæmoglobin.
4. " " carbon-monoxide hæmoglobin.
5. " " acid hæmatin in ethereal solution.
6. " " alkaline hæmatin.
7. " " methæmoglobin.
8. " " reduced hæmatin (hæmochromogen).
9. " " acid hæmatoporphyrin.

made of this fact in the estimation of the oxygen content of the blood. After the oxygen is discharged from oxyhæmoglobin, fresh oxygen, due to the oxidising action of the reagent added, takes its place; this new oxygen, however, is combined in some way different from that which was previously united to the hæmoglobin. (Haldane.)

This oxygen is not removable by the air-pump, nor by a stream of neutral gas such as hydrogen. It can, however, by reducing agents such as ammonium sulphide, be made to yield reduced hæmoglobin. Methæmoglobin is of a brownish red colour, and gives a characteristic absorption band in the red between the C and D lines (spectrum 7 in coloured plate). In dilute solutions other bands can be seen.

Carboxyhæmoglobin may be readily prepared by passing a stream of carbon monoxide or coal-gas through blood or through a solution of oxyhæmoglobin. It has a peculiar cherry-red colour. Its absorption spectrum is very like that of oxyhæmoglobin, but the two bands are slightly nearer the violet end of the spectrum (spectrum 4 in coloured plate). Reducing agents, such as ammonium sulphide, do not change it; the gas is more firmly combined than the oxygen in oxyhæmoglobin. CO-hæmoglobin forms crystals like those of oxyhæmoglobin. It resists putrefaction for a very long time.

Carbon monoxide is given off during the imperfect combustion of carbon such as occurs in charcoal stoves or during the explosions that occur in coal-mines; it acts as a powerful poison, by combining with the hæmoglobin of the blood, and thus interferes with normal respiratory processes. The effects of the formation of carboxyhæmoglobin have already been discussed (p. 261). The bright colour of the blood in both arteries and veins and its resistance to reducing-agents, are in such cases characteristic.

Nitric Oxide Hæmoglobin.—When ammonia is added to blood, and then a stream of nitric oxide passed through it, this compound is formed. It may be obtained in crystals isomorphous with oxy- and CO-hæmoglobin. It also has a similar spectrum. It is even more stable than CO-hæmoglobin; it is not only of theoretical importance as completing the series, but is of some practical interest in cases of poisoning by gas liberated from high explosives.

The Origin of Hæmoglobin.—As has been said, hæmoglobin belongs to the class of pigments known as porphyrins and contains iron; so also does the green chlorophyll of plants. Both are widely disposed in nature but not always in a form that can be utilised; but there is no evidence of this, for the body cannot break down the chlorophyll or even the iron-containing porphyrin, hæm. Articles of diet such as hare soup and black puddings made from blood are of no value as sources of iron to the body. The exact source

of the pyrrole remains unknown but the globin is probably synthesised.

If animals are bled, however, and given different foodstuffs we get an idea of the origin of the constituents of the blood generally, and from such studies it becomes evident that a meat diet is best for restoring hæmoglobin. For this, milk and its derivatives are of little use and carbohydrates valueless. Apricots and spinach are the best foods of vegetable origin, although it is obvious that the herbivorous animals must obtain their hæmoglobin from more usual sources. Most of such investigation has been carried out by Whipple and his colleagues in America on a standard anæmic dog which has had its total hæmoglobin reduced to about a quarter of its normal by hæmorrhage, and which is given a standard anæmic diet largely of carbohydrate to which the food under investigation is added. To a considerable extent the value of foods in this respect depends on the amount of iron they contain, although it is evident from the beneficial effect of drugs that the iron need not be in organic form. (See Iron.) Hæmoglobin formation is restricted by infections and this is one reason why if prolonged they lead to pallor of the face.

Blood Groups.

Ideally, the blood of another person is the best substitute for lost blood, but unfortunately all bloods are not compatible, but are liable to agglutinate or clump, and to hæmolyse, each other, and so cause serious symptoms and even death.

Blood groups were discovered by Landsteiner in Germany in 1900.

It has been found that individuals can be divided into four groups, according to the liability of their cells to be agglutinated. For practical purposes we can ignore the serum of the donor, since it is so diluted by the blood of the recipient. We have, therefore, to consider the effect of the serum of the recipient upon the corpuscles of the donor.

Group 1 or AB is the group of universal recipients; that is, its members can receive without causing agglutination cells of each of the other groups, but cannot give with safety to any but members of their own group. Individuals belonging to group 4 or O, on the other hand, cannot safely receive blood from any but their own group. Their blood can, however, be given to any other group and they are therefore known as universal donors.

Group 2 or A corpuscles are agglutinated by group 3 or B serum, but not by their own; while those of group 3 or B are agglutinated by group 2 or A serum, but again not by their own.

By having stocks of the serum of groups 2 or A and 3 or B, we can readily determine to which group any individual belongs; since 1 or AB is agglutinated by both, while 4 or O is not agglutinated by either. The tests are made by adding a little citrate to the unknown blood and mixing it with the standard sera on a glass slide or in a small test-tube. The agglutination will occur in a few minutes, if at all, and may readily be seen with the low power of the microscope.

Details of methods and the possible errors which may occur

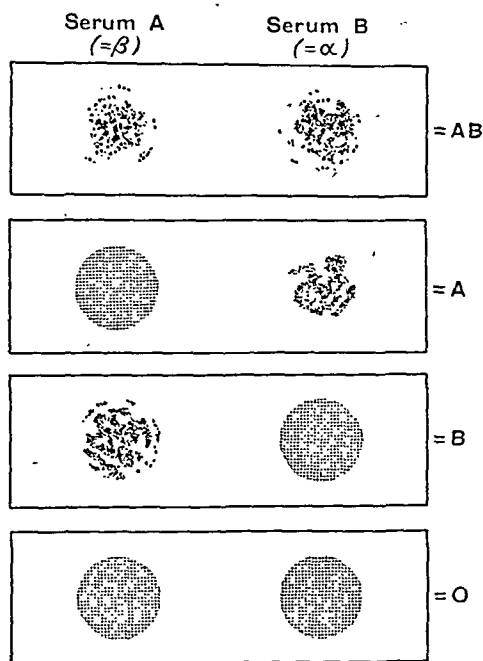


FIG. 140.—Diagram showing the effects of serums A and B on blood cells of different groups.

are given in War Memorandum of the Medical Research Council, 1942. (See also Weiner, 1943.)

Thus, if the blood, say of group 1, is injected into the blood stream or mixed with the blood of a recipient whose blood group is 4, it is first agglutinated (that is clumped) and subsequently hæmolysed. The presence of these specific hæmolysins and agglutinins in blood has led to the renaming of the blood groups as indicated in the table on p. 344. The + indicates agglutinin and - its absence in serum.*

* The cells agglutinated are considered to contain an iso-agglutinin. Thus group 2 contains A, and 3 has B. The injection of small amounts of incompatible blood greatly increases the incompatibility.

Group of Serum, <i>i.e.</i> recipient.	Group of donor, <i>i.e.</i> cells.				Percentage occurrence.
	1 AB	2 A	3 B	4 O	
1 or AB, <i>i.e.</i> with no agglutinin α . .	-	-	-	-	7
2 or A, <i>i.e.</i> with agglutinin β . .	+	-	+	-	40
3 or B, <i>i.e.</i> with agglutinin α . .	+	+	-	-	10
4 or O, <i>i.e.</i> with agglutinin α and β	+	+	+	-	43

The numbered classification is that of Moss, which has now been largely superseded by the original of Landsteiner in letters which are indicative of the agglutinin content. Group A has now been subdivided into A_1 and A_2 giving A_1B and A_2B . The subgroup A_2 differs from A_1 in that it reacts much more weakly and not in high dilutions (over 1/16).

When plasma only is being given the blood groups may be ignored as it becomes so diluted by the blood of the recipient.

Blood groups are inherited and form a basis for determining parentage and for studying racial distribution. Any given child cannot have a parent who could not have contributed to his group. Thus parents who belong to O cannot have children of groups AB, A or B, nor can two B's produce A children, and *vice versa*.

Rh Factor.—The presence of this factor was discovered by testing samples of human blood with the serum of rabbits into which had previously been injected the blood of a rhesus monkey. It was found that irrespective of group the blood of some 85 per cent. of humans was agglutinated (*i.e.* Rh positive) and that of 15 per cent. Rh negative. The transfusion of positive with negative subjects may therefore produce reactions, especially if repeated as the negativity is increased. The factor is inherited and its importance lies in the fact that the mother may by absorption become immune to the blood of the foetus and suffer from reactions if transfused after childbirth especially if the child suffers from erythroblastosis (excess of red cells commonly associated with jaundice). Patients suffering from other diseases may develop a self-immunisation. The presence of this factor emphasises the desirability of direct checking of blood before transfusion.

Hæmolysis.

We have already seen that hæmolysis of the red blood-corpuscles takes place if they are exposed to distilled water, but they may be broken up in a variety of ways. (See Ponder, 1924 and 1934.)

1. By hypotonic solutions (see Fragility above).

2. By mechanical crushing. This is very liable to occur if blood is pumped outside the body.
3. By fat solvents like chloroform or ether which dissolve the cell membrane.
4. By substances which lower surface tension such as bile salts and saponin.
5. By diverse agents, *e.g.* alternate heat and cold, ultra-violet rays, changes in reaction of surrounding medium, some snake-venoms, etc.
6. By specific **hæmolysins**. If the blood of animal A is injected into animal B of another species, the blood of B develops specific hæmolysins and becomes capable of very rapidly destroying the corpuscles of A if they are subsequently injected.
7. By natural hæmolysins as in the blood groups which are discussed below. Before actual hæmolysis takes place there is an agglutination of the corpuscles.

Tests for Blood.—Briefly, these are microscopic, spectroscopic, and chemical, and it is well to remember that in testing for blood in the fæces in cases of suspected gastric or intestinal ulcer it is necessary to place the subject on a meat-free diet for a few days prior to the test. The best chemical test is the formation of hæmin crystals, but the spectroscopic test for hæmochromogen is probably the most delicate. Both are used in medico-legal work. The old test with tincture of guaiacum and hydrogen peroxide, the blood causing the tincture to become bluish green, is very untrustworthy, as it is also given by many other organic substances. The test, for instance, is given by milk, and is there due to the presence of an enzyme called a peroxidase, which is destroyed by boiling. Boiled blood, however, gives the test as well as fresh blood, and the reaction is due to the presence of the iron-containing radical of hæmoglobin. In Adler's modification of this test, benzidine dissolved in glacial acetic acid takes the place of tincture of guaiacum.

In testing whether or not a red fluid or stain on clothing is of blood, in a medico-legal case, it is advisable not to rely on one test only, but to try every means of detection at one's disposal. To recognise blood is usually easy, but to distinguish human blood from that of the common mammals is possible only by the "biological" test. (See Specific Hæmolysins below.)

The Storage of Blood and Blood-Plasma.—It is possible to store blood at low temperatures for a few weeks, and this has been found very valuable for the emergencies of war time. It is apparently safe to keep blood for a month without any deleterious effects, but thereafter the older corpuscles die and the oxygen-carrying power of the blood is affected. Slowly methæmoglobin is

formed. The blood must be kept sterile but not frozen or the corpuscles will break up. To avoid this difficulty, extensive use has been made of stored blood-plasma and of dried or concentrated plasma, which has the advantage of portability; it is diluted with water as required. It is dried in a vacuum at a low temperature to avoid the coagulation of its protein. Fluid plasma, however, may, after a month, develop a toxic peptone with choline-like properties (Gilding); but how far this is present in sufficient quantities to be important is a matter of debate.

Blood Substitutes.

The physiological characteristics of blood must be considered from the point of view of substitutes which may be required to replace blood lost by hæmorrhage. (See Doan, 1927.)

If a suitable blood from another individual is not available to replace the lost blood, the fluid used must be as like the original as possible. In order to achieve this the fluid must contain sodium, potassium, calcium, and bicarbonate, as in Ringer's solution. Such a substitute would not, however, stay in the vessels, as it has not the requisite osmotic pressure. It is impossible to make up this pressure with additional salts, since these merely become excreted by the kidney, or escape into the tissues. As we have seen, an important factor in keeping the blood in the vessels is the osmotic pressure of the proteins, which normally counteracts the blood-pressure in the capillaries, which tends to force the fluid through the capillary walls. It is necessary to give a substance which is inert yet will supply the required osmotic pressure and viscosity.

It should be emphasised, however, that the injection of large quantities of plasma or saline solution is unjustifiable. If large quantities of fluid are needed hæmoglobin must also be required.

Further, it has been shown that when the blood-pressure has fallen because of a loss of peripheral resistance the injection of fluid cannot raise it to normal and the body simply becomes waterlogged.

Immunity.

While strictly speaking immunity is part of Physiology, it is so closely related to reactions to bacterial invasion of the body that by convention it is now considered part of the subject of Bacteriology.

CHAPTER XXIII

GENERAL METABOLISM AND ENERGY EXCHANGES

IN general metabolism we consider the total amount of energy exchange which is going on in the body under varying conditions. That these exchanges are associated with a consumption of oxygen proportional to the activity of the body was first recognised by Lavoisier in Paris in 1780.

Energy.—When the fuel in an engine's furnace is burnt, there is no real destruction of matter, for the products of combustion (CO_2 , etc.) are equal in weight to the original fuel, *plus* the oxygen of the air which has entered into combination with it. During this combustion or oxidation, energy is liberated, and energy, like matter, is also indestructible though it exhibits transformations. In the unburnt fuel the energy is latent or potential, but as the coal burns three forms of actual energy or force are liberated: one of these is *light*, another is *heat*, and the third is *mechanical work* which makes the wheels go round. There is a fixed relationship between these forms of energy; heat, for example, can be transformed into mechanical work, but always in a definitely fixed proportion. Energy may be measured in terms of foot-pounds, horse-power, or in heat-units, as is done by gas companies and in physiology.

The Calorie * (the large calorie) is the amount of heat required to raise the temperature of one kilogram of water from 16° to 17° Centigrade, and the instruments which measure the calorific value of substances are called calorimeters.

The data necessary for the study of the energy exchanges of the body are determined by the process known as **calorimetry**.

The Bomb Calorimeter.—The heat of combustion of any of the food substances or of the excreta was originally carried out directly by an apparatus known as the bomb calorimeter. It consisted essentially of a chamber or bomb surrounded by a water-jacket in which the food was set alight by an electric current in an atmosphere of oxygen. The heat produced could be calculated from

* The British Thermal Unit is 251.9 small calories and is the amount of heat required to raise one pound of water from 60° to 61° F. A therm is 100,000 of these. The small calorie is a unit in which 1 gram takes the place of the kilogram (1000 grams) in the large calorie.

the rise in temperature of the water, allowance being made for the heat produced by the current itself.

It has been found in practice, however, that it is very difficult to avoid heat-loss from such an apparatus and generally it is most

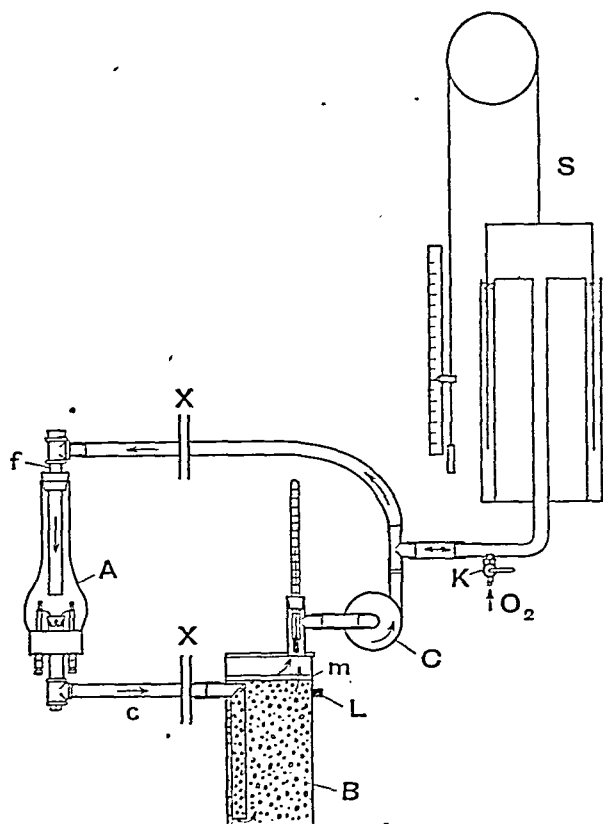


FIG. 141.—Diagram of the apparatus used for indirect calorimetry. S, spirometer for oxygen, which can be replenished through K. C, a fan to maintain the circulation of the gases. B, soda-lime to absorb carbon dioxide. At X may be attached a small chamber (A), in which food may be burned electrically, a small animal housed, or a mouth-piece for man. The fall in the volume of oxygen in the spirometer indicates the amount used. (Benedict.)

convenient to apply the method of *indirect calorimetry*. This consists essentially of measuring the oxygen used in oxidising the fuel and calculating the heat produced. The apparatus described (fig. 141) is that used by Benedict at the Carnegie Nutrition Laboratory in Boston. It consists essentially of a small glass chamber (A) in which combustion by means of electricity is carried out and to which is connected a spirometer containing oxygen. The gases are kept circulating by means of a fan and the carbon dioxide evolved is absorbed by soda-lime. The reduction in the amount of oxygen can be read off.

Any given oxidation will always produce the same amount of heat.

Thus, if we oxidise a gram of carbon, a known amount of heat is produced, whether the element is free or in a chemical compound. The following figures show the approximate number of Calories produced by the combustion of 1 gram of the following substances:—

Fat average	9.3	Starch	4.2
Carbohydrate average	4.1	Glucose	3.7
Protein in body	4.1	Cane-sugar	3.9
Protein in calorimeter	5.6	Alcohol	7.08

It is, however, most important to remember that the "physiological heat-value" of a food may be different from the "physical heat-

value," *i.e.*, the amount of heat produced by combustion in the body may be different from that produced when the same amount of the same food is burnt in a calorimeter. Incompletely burnt products of protein metabolism such as urea, uric acid and creatinine are excreted in the urine and faeces, and a small amount of heat is required for the solution of the protein and its products. When these are allowed for, the calorific value of protein is practically that of carbohydrate (Rubner). This is a fact which is not generally appreciated. The taking of proteins is an unnecessary and very expensive way of supplying calories to the body although they have important values in other respects. No difference between the physical and physiological heat-values of fats and carbohydrates exists, provided, of course, that all the fat and carbohydrate in the food is absorbed. The figures indicate that fat is a much better source of energy than carbohydrate and that it is also the better method of storing energy from the point of view of weight.

The energy transformed in the body is also expressed as heat. Other forms of energy, such as physical work, must also be taken into account, one small calorie being equivalent to 426.6 gram-metres.

Methods of Studying Metabolism.—We may study metabolism or the burning of fuel in the body just as we may study the burning of food outside the body, that is, directly or indirectly. In the former, we find the amount of heat produced by the body under varying conditions: in the latter, we find the amount of oxygen consumed in a given time and from our knowledge of the nature of the fuel which is being oxidised in the body we can arrive at an idea of the amount of heat produced.

The **direct method** consists of putting the individual or animal into a calorimeter. The heat produced indicates the rate of the general metabolism, but as has been said the difficulty of preventing loss of heat from such apparatus is so great that they have now largely been given up. They are, however, of considerable historic interest since all the basal work was done with them.

The original calorimeter was invented by Atwater with the assistance of the physicist Rosa and improved upon by Benedict. It was capable of measuring a given amount of heat generated electrically with great accuracy.

The *Atwater-Benedict Respiration Calorimeter* (fig. 142) consists of a room with non-conducting walls. Through this run coils of water-pipes, fitted with metal discs. Only one of these tubes is shown in the figure (A). Any rise of the temperature of the room is at once taken up by the discs and communicated to the water. The whole of the heat production of the individual in the calorimeter is therefore spent in raising the temperature of the water. The amount of water which goes through the pipes multiplied by the difference in the temperature of the water as it enters and as it leaves the calorimeter, gives the heat output of the person within it. This temperature is ascertained by the thermometers (T , T).

In the food calorimeter it is possible to ensure the complete combustion of the substance placed in the chamber. It is not possible to ensure the complete oxidation of the food eaten. For instance, food may be retained and assimilated

with a gain of weight to the individual. This difficulty is met in the following way. The air of the calorimeter is kept circulating through a series of chambers in which the carbon dioxide and the water are absorbed, and subsequently estimated. As the oxygen is used up by the individual, fresh oxygen is admitted in known quantities. The urine and faeces are analysed as well as the air, at the beginning and end of the experiment. The following additional data are therefore forthcoming: (1) the carbon, hydrogen, and nitrogen given out by the body; (2) the oxygen taken in, and from these the amounts of protein, fat, and carbohydrate metabolised in the body, can be calculated. The apparatus combines therefore the direct and indirect methods of studying metabolism.

In the calorimeter is a bicycle, the hind wheel of which is replaced by or connected with an arrangement, *e.g.* a dynamo or a hand brake, by which the amount of work done can be measured.

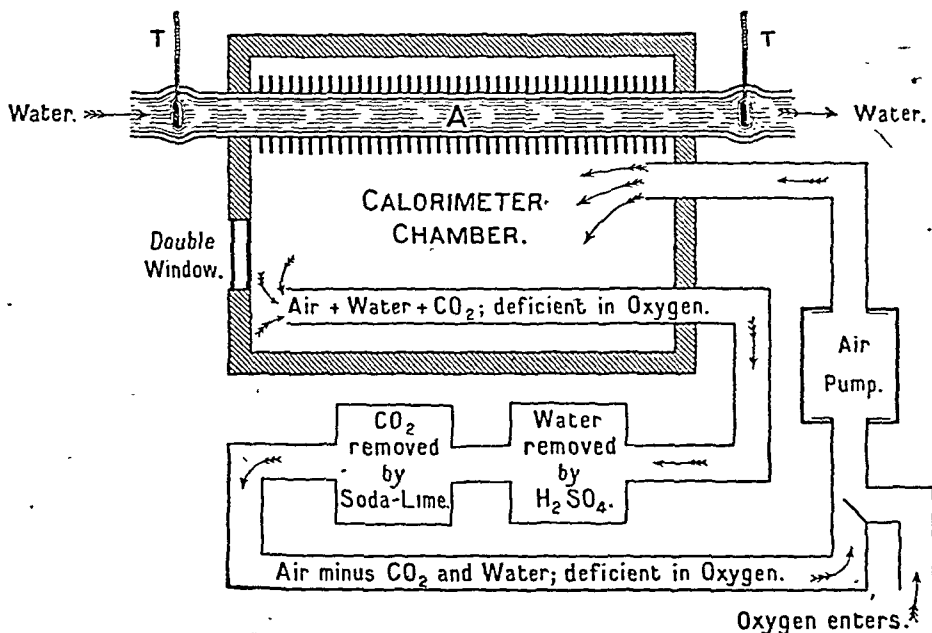


FIG. 142.—The Atwater-Benedict calorimeter.

The calorimeter is also supplied with a bed, a table, a chair, and a double window, through which food of known weight and composition can be supplied, so that an experiment may continue over two or three days, and the effect of work, sleep, various diets, etc., can be studied.

The *Benedict differential calorimeter*, now the only direct calorimeter used, is in some degree a simpler apparatus in which the heat given off is measured by finding the amount of heat (generated electrically) which must be supplied to keep the temperature of a control chamber up to that containing the animal or man. Both chambers are enclosed in a common outer chamber and differences in their temperatures are recorded electrically. This calorimeter is less liable to be affected by accidental errors such as leakage than the Atwater-Benedict type, which it has generally replaced.

Indirect Methods.—These are the most convenient methods and are extensively used in the investigation of disease. In all, the

amount of oxygen used in a given time is determined and the number of calories produced calculated therefrom.

Benedict's Method is that most extensively used clinically; the individual breathes, for a given time, to and from a spirometer containing pure oxygen, the carbon dioxide of the expired air being absorbed by passing it through soda-lime. The oxygen used may then be read off directly from the spirometer. (See fig. 143.)

The apparatus is essentially the same as that for the indirect calorimetry of foods except that the apparatus is larger and the oxidation chamber connected at X in fig. 141 is replaced by a suitable mouth-piece or head-piece. In the case of small animals the oxidation chamber may be of such a size as to contain the animal. Such a method was originally used by Haldane and Pembrey, who calculated the metabolism from the increase of weight of the soda-lime. For man the indirect method may be used in conjunction with the differential calorimeter described above.

The Douglas Bag Method has the advantage of portability, and therefore can be used while the subject is employed at a variety of tasks. In this method the expired air is collected in a Douglas Bag over a given period, say of ten minutes. A sample is analysed, usually by the Haldane method, and the volume obtained by passing the contents of the bag through a gas meter. The amount of oxygen consumed (usually 300 to 400 c.c. per min.) is obtained by subtracting the amount of oxygen found in the bag from that in the normal air. Several corrections for temperature and water vapour have to be made in making the actual calculation, but these need not concern us here. They are usually taken from tables.

Having found the amount of oxygen consumed in ten minutes by any of these methods, we calculate the calories produced in 24 hours. This depends on the nature of the fuel utilised. It must be realised that this is not necessarily the fuel taken in by the mouth, but also that previously stored in the tissues. It has been determined by burning food in a limited quantity of oxygen that, if carbohydrate is being burnt, 1 litre of oxygen produces 5.05 Calories, if fat 4.6 and if protein or a mixed diet 4.8. For practical purposes the average may be taken as 5 calories, for the variation in the metabolism of an individual from causes such as nervous tension and muscular relaxation introduces such a large error that only large variations are of clinical significance.

In more accurate research work it is necessary to take into consideration the respiratory quotient (R.Q.), i.e., $\frac{\text{CO}_2 \text{ given out}}{\text{O}_2 \text{ used}}$, see p. 288, which gives an indication of the relative amounts of carbohydrate and fat being burned. The reason for this is as follows. If carbohydrate was being burned, e.g. glucose ($\text{C}_6\text{H}_{12}\text{O}_6$), all the oxygen lost would appear again as carbon dioxide (CO_2) in the expired air, since the carbohydrate itself contains sufficient oxygen to oxidise its

own hydrogen. The respiratory quotient would therefore be unity and a litre of oxygen would have a heat equivalent of 5.05 Cal.

If, however, a fat was being consumed, *e.g.* tristearin $C_{57}H_{110}O_6$, oxygen would also be used in oxidising the hydrogen to form H_2O . Thus, the amount of oxygen taken in would become larger than the amount of carbon dioxide expired and the respiratory quotient would become less than unity and the heat equivalent less than 5, *e.g.* an R.Q. of .7 would mean that a litre of oxygen produced 4.6 C.

On a mixed diet the R.Q. is about 0.82, and since protein is about the average its effect on the quotient need not be considered.

The higher the respiratory quotient (*i.e.* the more carbohydrate is being used) the more heat is produced by a litre of oxygen.

It is necessary also to introduce a correction for the oxygen lost in oxidising hydrogen and which is lost as water. If the expired air contains 4 per cent. CO_2 and 16 per cent. oxygen the remainder, 80 per cent., must be nitrogen. Since the atmosphere contains 79.06 per cent. N, it is evident that more oxygen per cent. must have been absorbed than appears, *i.e.* $20.94 \times \frac{80}{79.06} = 21.19$, from which the amount of oxygen in the expired air must be subtracted in calculating the actual oxygen used.

A correction must also be made in measuring the expired air for its increased temperature and water vapour, for all gases must be measured dry at $0^\circ C$. and 760 mm Hg. This is usually done from tables.

Basal Metabolism.—This is the metabolism which is necessary to maintain the essential functions when the individual is in a state of mental and physical rest, preferably asleep, during which work (internal work) is done by various internal organs to maintain life; cardiac activity, respiration, body temperature, for example, must be maintained. It varies with size, age, and sex, but for the average young adult it may be taken as **1700 calories**. In certain conditions, notably hyperthyroidism, the basal metabolic rate may be increased.

Small individuals and animals have a higher basal metabolism *per unit of body-weight* than large animals, as they have a relatively greater body surface from which heat is lost.

For purposes of comparison metabolism is calculated in terms of calculated body surface which is $\text{weight } 0.425 \times \text{height } 0.725 \times .007184$.

It is found that the average young man produces about **40 calories per square metre of body surface** per hour. This is about 1 calorie per kilogram per hour. For practical purposes it may be noted that the basal metabolic rate is proportional to the heart rate in the same circumstances. (See Talbot, 1925.) The rate for women is slightly higher in young women and lower in older.

The Metabolic Rate depends chiefly on the physical activity of the individual, as is seen by the following table:—

Man in bed 24 hours uses and requires	
(basal metabolism)	1,680 large calories.
In bed 8 hours, sedentary occupation for	
16 hours	2,170 „

Bed, 8 hours; in a chair, 14 hours;
 walking, 2 hours 2,500 large calories.
 Active outdoor life 3,500
 Rider in a 6 days' bicycle race per day . 10,000 ,,

It can then be said that for a given subject the metabolic rate indicates the amount of body tissue in activity.

These figures are of very great importance since on the basis of them a nation may be rationed in time of stress and the diet

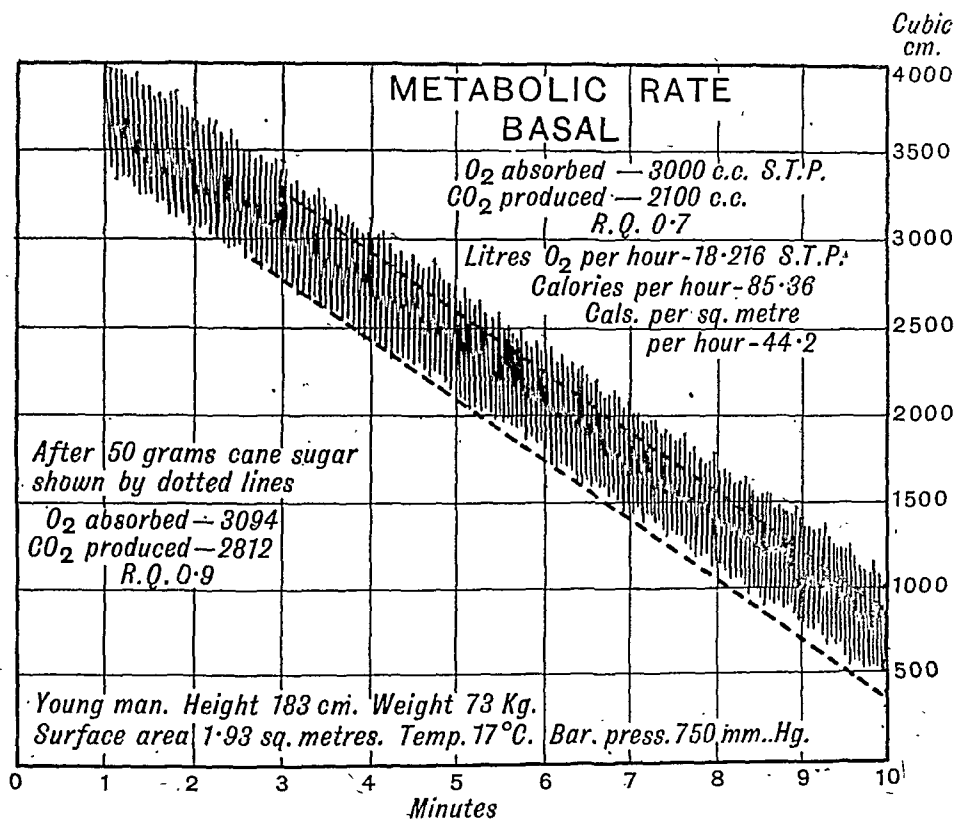


FIG. 143.—A typical record of metabolic rate taken by a spirometer (see fig. 98).* The dotted line indicates the increased rate caused by taking glucose (from records kindly supplied by Gilding).

of the individual adapted to his needs, which are indicated by his metabolic rate. Fuel must be supplied to replace that burnt, otherwise the body will consume its own stores and become wasted. (See Diet below.) The first accurate experimental studies in such subjects were published by Liebig in 1842, but the foundation of all calorimetric work was laid by Voit who in the latter half of the nineteenth century founded the Munich School. This was greatly extended by his pupil Rubner, subsequently of Marburg

* With the more elaborate Benedict spirometer the position of the writing lever causes the record to read from below upwards.

Of recent years such studies have been largely concentrated in Benedict's laboratory in Boston, U.S.A. (See also Newburgh, Johnston, and others; also Du Bois, 1936.)

The diet itself may affect the metabolic rate, particularly the amount of protein taken, for all food stimulates metabolism. This is known as the specific dynamic action of food and is discussed further below. External cold also increases the rate.

The Control of the Metabolic Rate.—The metabolic rate is controlled through the agency of certain ductless glands, especially the thyroid.

THE THYROID GLAND.

The thyroid gland is situated in the neck. It consists of two lobes, one on each side of the trachea; these lobes are connected across the middle line by a middle lobe or isthmus. It is highly vascular.

The gland is encased in a capsule of dense areolar tissue. This sends in strong fibrous trabeculae, which enclose the thyroid *vesicles*—which are rounded or oblong sacs, consisting of a wall of thin hyaline membrane lined by a single layer of short cylindrical or cubical cells. These vesicles are filled with transparent colloid nucleo-protein material. The colloid substance increases with age, and the cavities appear to coalesce. In the interstitial connective-tissue is a capillary plexus, and a large number of lymphatics.

Function.—It has been definitely established that the thyroid gland regulates the metabolic rate, and in the young, the growth of the body. This conclusion has been arrived at by observations, both on man and on animals.

The Effects on Metabolism.

The Effect of Thyroid Deficiency (Hypothyroidism). — This condition may be produced experimentally in animals; it may occur spontaneously, or be produced surgically in the human subject. The **basal metabolism** becomes very low and the outstanding feature is slowing down of mind and body. There is, as a result, an accumulation of fuel in the form of fat, the pulse slows, and in man there is peculiar degeneration of the subcutaneous tissues which has caused the condition to be called *myxœdema*. The face and hands become grossly swollen, and this, together with the accumulation of fat, makes the body very unwieldy. The skin is dry and scaly and the hair falls out. The mentality is dull and the patient answers simple questions very slowly. The condition is completely cured by the administration of extract of thyroid from other animals. (See fig. 143A.)



As first seen



After 5 weeks' treatment.



After 15 months' treatment.



After nearly 30 years' treatment.

Case of Myxœdema showing the beneficial effect of thyroid extract over a long period of years.
(From the originals of Raven.)



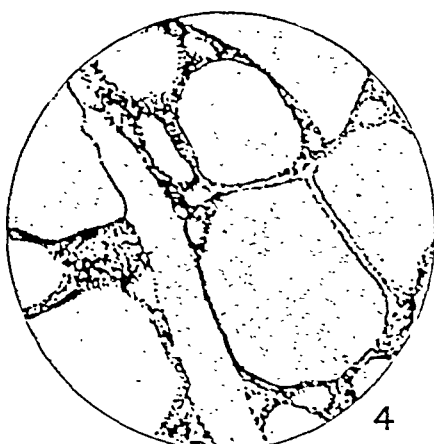
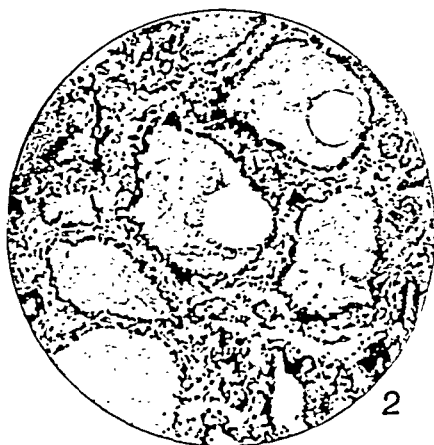
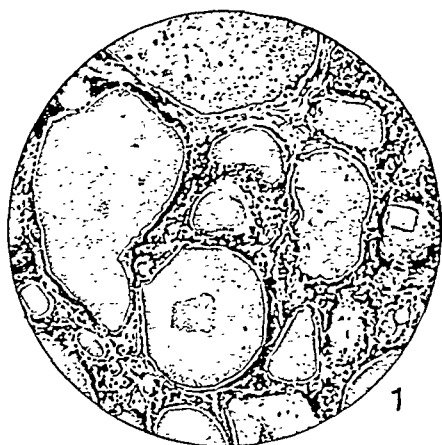


FIG. 143B.—Illustration of differing degrees of thyroid activity.

1. Normal. 2 and 3. Increased action as in hypothyroidism. 4. Colloid goitre.
(After Marine, by permission of *Journ. Amer. Med. Assoc.*)

When the condition occurs in a child the disease is known as *cretinism*, in which the subject is commonly an idiot and a dwarf, with all the characteristics of slowed metabolism. It was, indeed, the similarity between this state in the child and the state produced by surgical removal of the organ in man, which led to the discovery of the function of the glands, especially after Schiff the physiologist had demonstrated that surgical removal of the whole gland in dogs was followed by death. Nowadays, the whole of the gland is not removed. Cretins, which were usually the children of myxœdematous mothers, are now very rare.

Nothing is more striking than the way in which cretins who otherwise would be idiots, under the influence of thyroid extract, grow into useful members of society. Here, as in the treatment of myxœdema, the results of experimental investigation (for the facts were not fully established until Schiff performed his experiments on dogs) have proved of the greatest service to mankind.

The Effect of Thyroid Excess (Hyperthyroidism).—This occurs when the thyroid becomes excessively active in man, and rarely from excessive administration of the extract. There is an increased activity of mind and body. The nervous system is hyperexcitable, e.g. the reflexes are increased and there are fine tremors of the hands. It is this excitability which commonly draws attention to the state. The **metabolic rate** is markedly above normal; the individual uses up all his stores of fuel and becomes thin; the heart rate becomes excessive; there is sweating. In man there is often produced a characteristic protrusion of the eyeballs, which has caused the name *exophthalmic goitre* to be given to the condition (fig. 143A). This does not occur when the hyperthyroidism is caused by administration of the extract, but is produced in animals if the long-acting sympathetic stimulant ephedrine is administered. The protrusion of the eye is caused by the contraction of the smooth muscle in the connective tissue behind and around the eyeball. Death occurs from exhaustion, especially of the heart, but is prevented by partial removal of the organ or its destruction by X-rays.

The success of such treatment furnishes complete proof that the disease is really due to the thyroid, but it has also been found that the blood of patients suffering from the condition has, like thyroid extract, the power of protecting mice against the poisonous effects of aceto-nitrile (CH_3CN).

The Relation of the Thyroid to Growth.—In young animals in which the thyroid has been removed, as in children in whom the thyroid is deficient, there is a marked retardation of physical and mental growth.

The effect on growth appears to depend not wholly on metabolism,

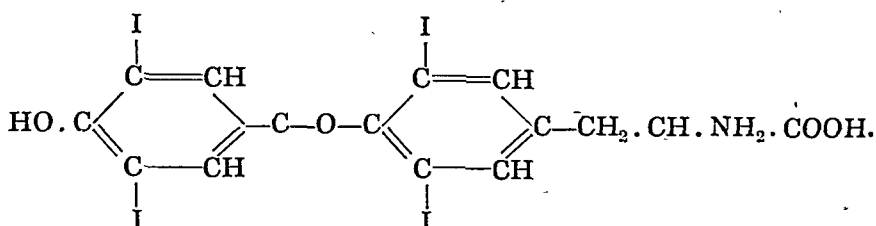
but also on the relationship of the thyroid to the growth of cells. It is found that tadpoles fed on thyroid develop much more rapidly into frogs, although smaller than normal, than do controls not so fed (Gudersnatch). Indeed, this is now a usual method for standardising thyroid extract. The Mexican axolotl, which in nature remains permanently in the tadpole stage, develops proper legs and becomes a land animal under the influence of thyroid. The administration of iodine appears to have a similar effect, which is probably due to an increase in the ease with which thyroxine can be elaborated since the effect depends on the presence of the thyroid.

The activity of the thyroid is closely linked up, as shown particularly by Marine, with the metabolism of iodine, interference with the supply or absorption of which may lead to a form of thyroid disease known as simple goitre, which is a swelling of the gland due, apparently, to an accumulation of colloid material, but not necessarily associated with any symptoms. It is specially prevalent where chalk abounds, as in Derbyshire, and in many districts iodine is administered to children as a preventive measure. M'Carrison has shown that simple goitre may be produced by infection and thus explained the occurrence of so-called goitre wells. He showed that if fishes so infected were placed in the middle of three pools through which water flowed from one to the other, the fishes below were infected but not those in the pool above. Apparently bacterial conditions may occur in the intestine, which interfere with the absorption of iodine and in such cases the goitre may be kept in check by the use of intestinal antiseptics such as thymol. He has also emphasised the rôle of the diet in the causation of goitre, especially of fats which tend to fix iodine, and a certain variety of American cabbage. Goitre is also produced by the injection of an alkaline extract of the anterior lobe of the pituitary body. Iodine will not, however, cure the goitre of scurvy or a variety which is brought about by ligature of the pancreatic duct. Small doses of iodine are also found to be of definite advantage in exophthalmic goitre, but the effect is temporary.

Thyroxine.

Long before the above facts were known it was realised that the thyroid gland contained iodine in varying amounts according to the diet of the animal. Delicate chemical methods have shown that many of the common articles of diet (milk, eggs, onions, carrots, etc.) contain this element in sufficient quantities for our needs. It has now been shown that the active principle of the thyroid contains iodine in conjunction with the amino-acid tyrosine, and it has

been possible to produce thyroxine synthetically (Harington). Its formula is—



This should be compared with the formula of tyrosine on p. 286. This constitution of thyroxine emphasises the importance not only of iodine but also of tyrosine in the diet. Thyroxine is excreted in the bile.

The action of thyroxine can apparently be antagonised by the pyrimidine, **thiouracil**, a derivative of nucleic acid.

The drug has now been successfully used for the alleviation of hyperthyroidism although it has no permanent effect on the condition. The use of thiouracil is not, however, free from risk.

The Control of Thyroid Activity.

The thyroid is probably thrown into activity by the sympathetic, since stimulation of this nerve or the injection of adrenaline causes a current of action to be produced in the gland, while if an animal is exposed to cold which increases sympathetic activity and the gland examined it is found to be very active, as indicated by a large number of cells and a relatively small amount of colloid. It has been shown, too, that animals deprived of their thyroids die particularly readily from exposure to cold. It may therefore be considered that the function of the thyroid is to adjust the metabolic rate to the needs of exercise and body temperature. Increased secretion, however, has not yet been demonstrated. It has been claimed that some cases of exophthalmic goitre have resulted from fright, but the most suggestive experiments regarding the control of the thyroid by the sympathetic are those of Cannon, who obtained the symptoms of hyperthyroidism by anastomosing the phrenic with the peripheral end of the cervical sympathetic. The administration of anterior pituitary causes increased thyroid activity and growth and there appears to be an inhibitory control by the adrenal cortex.

The Conservation of Energy.

From calorimetric studies it becomes evident that the Law of the Conservation of Energy is applicable to the animal body.

The following table exhibits the relation between the production and discharge of energy in twenty-four hours in the human organism at rest, estimated in calories. The table conveniently takes the form of a balance-sheet in which production and discharge of heat are compared; to keep the body-temperature normal these must be equal. The basis of the table in the left-hand (income) side is that recommended by Voit.

<i>Production of heat.</i>			<i>Discharge of heat.</i>		
Metabolism of		Large Calories.			Large Calories.
Protein (120 gm.)	120×4	= 480	Warming water in food,		
Fat (100 gm.)	100×9.4	= 940		$2.6 \text{ kilos} \times 25$	= 65
Carbohydrates			Warming air in respiration,		
(= 333 gm. starch))	333×4.16	= 1385		$16 \text{ kilos} \times 25 \times 0.24$	= 96
			Evaporation in lungs,		
				$630 \text{ gm.} \times 582$	= 366
			Radiation, evaporation, etc.,		
			at surface, <i>plus</i> the thermal		
			equivalent of mechanical		
			work done accounts for the		
			remainder		
					2278
					<u>2805</u>
		<u>2805</u>			

The figures under the heading Production are obtained by multiplying the weight of food by its physiological heat-value. The figures on the other side of the balance-sheet are obtained as follows: The water in the food is reckoned as weighing 2.6 kilos. This is supposed to be at the temperature of the air, taken as 12° C.; it has to be raised to the temperature of the body, 37° C., that is, through 25° C. Hence the weight of water multiplied by 25 gives the number of calories expended in heating it. The weight of air is taken as 16 kilos; this also has to be raised 25° C., and so to be multiplied by 25; it has further to be multiplied by the specific heat of air (0.24). The 630 grams of water evaporated in the lungs. must be multiplied by the potential or latent heat of steam at 37° C (582); the portion of heat lost by radiation, conduction, and evaporation from the skin constitutes about four-fifths of the whole, and is obtained by deducting the three previous amounts from the total. This table does not take into account the small quantities of heat lost with urine and faeces. If the man does external work the amount of energy dissipated is increased, and he would, in consequence, require more to be supplied in the form of food. Very few men in active work get on well with a smaller supply than 3500 calories in their diet.

We may state the general results of experiments of this nature as follows:—

1. If an animal is doing no external work, and is neither gaining nor losing substance, the potential energy of the food (expressed as

its heat of combustion) will be equal to that of the excreta, *plus* that given off as heat, *plus* that of internal work.*

2. If an animal is doing external work, and is neither gaining nor losing substance, the potential energy of the food will be equal to the heat of the excreta, *plus* that given off as heat, *plus* that of the internal and external work.

3. If an animal is doing no external work, but gaining or losing body-substance, the potential energy of the food will equal the potential energy of the excreta, *plus* that given off as heat, *plus* that of the internal work, *plus* that of the gain by the body-substance (a loss by the body being regarded as a negative gain).

4. In an animal doing external work, and gaining or losing body-substance, the potential energy of the food will equal the potential energy of the excreta, *plus* that given off as heat, *plus* that of the internal and external work, *plus* that of the gain (positive or negative) of the body-substance.

Of the heat produced in the body, it was estimated by Helmholtz that about 7 per cent. is represented by external mechanical work, and that of the remainder about four-fifths are discharged by radiation, conduction, and evaporation from the skin, and the remaining fifth by the lungs and excreta. This is only an average estimate, subject to much variation, especially in the amount of work done.

Body-Weight depends on the relative amount of energy taken in and lost—potential energy being stored in the form of fats. In the young the income exceeds the expenditure and the body gains in weight, but a balance is usually arrived at later. The law of the conservation of energy holds in relation to stout persons whatever their own opinion of the matter! Many simply eat too much.

To gain weight it is necessary to take in more calories than are expended. Children often expend large amounts of energy and since their body surface is relatively large the smaller they are the faster their basal metabolic rate.

To lose weight the reverse is necessary and in order to satisfy the appetite, foods such as fruit and green vegetables are taken rather than fats and carbohydrates. Proteins free from fat are to be preferred to carbohydrates because of their stimulating effect on metabolism. Sometimes thyroid extract is taken as a metabolic stimulant, but care must be taken because of its cardiac effects. A pulse rate over 100 may be regarded as a danger signal. Whatever the methods used to change the body-weight it should be emphasised that the process should be gradual or it becomes unsafe.

It is, however, well known that some normal individuals cannot get fat or thin at will. There is little difference in their basal

* If we include the excreta we do not include the warming of food.

rate, but apparently there is considerable variation in the response to protein, the thin person being unduly stimulated by it.

Abnormal increase of body fat occurs in deficient activity of the thyroid gland and the pituitary body which affects carbohydrate metabolism.

The requirements of the young in regard to body-weight are more extensive than those of the adult, for materials have to be taken in to support growth. As will be seen later, in addition to sufficient calories an optimal protein and salt intake is necessary and vitamins specially needed for growth must be supplied.

The Extraneous Factors in Dietetics.—It should, however, be pointed out that in dietetics much more has to be considered than calorific and protein value and these are of great importance to the practising physician. For example, a diet with no fat tends to be digested and absorbed rapidly and is, therefore, not satisfying, and results in hunger between meals. On the other hand, excessive fat, especially in some individuals, results commonly in dyspepsia because it reduces stomach movements and the secretion of gastric juice, but later leads to an increase when the stomach is empty. Fried foods are, therefore, less desirable for sick persons than boiled. Fatty fishes, like herring and mackerel, have a similar disadvantage. The quality of the water also affects nutrition. Notably water containing much calcium tends to interfere with the absorption of iodine and to produce goitre, and there seems little doubt that this factor is of greater importance than is generally recognised.

Finally, there is the individual variation which has been referred to above in relation to body weight. There is also a considerable variation in digestive capability, which may be inherited or acquired, and also abnormal (allergic) reactions to specific foods may be present.

CHAPTER XXIV

DIET

The Quality of the Diet.—From what has been said of the chemical constitution of the body, it is evident that a large variety of substances must be supplied to nourish the body adequately. They are:—(1) Protein, the most important constituent of meats. (2) Carbohydrate, contained in starchy and sugary substances. (3) Fats. (4) Water. (5) Salts. (6) Vitamins. It is only of recent years that the importance of the latter two constituents has been realised, but it has rapidly become apparent that they are important out of all proportion to the amount taken. It may indeed be said that the kind of food taken requires as much consideration as the amount. The differentiation of foods into their different classes was, however, made by Magendie as early as 1820.

General and convenient discussions of the subject of nutrition in general are given by Graham Lusk, in whose classical work much of historical interest is given, by Sherman and Lanford, and by Nixon and Nixon.

As originally pointed out by Liebig, food is necessary to build up tissue and to act as a source of energy. The former function is more particularly the duty of the protein of the diet, the latter is performed for the most part by the fats and carbohydrates.

The water is necessary to promote the solution of substances during absorption, metabolism, excretion, etc., while the salts and accessory substances act as general regulators of body processes.

It is also important that the foodstuffs should be provided in a digestible form. As an instance of this many vegetables, notably peas, beans, lentils, contain even more protein than beef, but they are not so nutritious, as they are less digestible, much passing out in the faeces unused.

The food also must have a **certain minimum bulk**, in order that it may stimulate the intestine and so be propelled along the gut. Most natural foods contain a certain amount of indigestible material or roughage, such as cellulose, which is not much affected by the digestive juices and which keeps up the bulk of the intestinal contents. Unfortunately, many modern foods, *e.g.* white flour, have this roughage removed by purification, and it is claimed that this is responsible for constipation. When such

articles of diet are eaten the necessary roughage should be added in the form of fruits and vegetables which contain cellulose.

In considering the amounts of the various body requirements we may roughly compare the body to a steam engine. To maintain this in order it is necessary to supply it with fuel and also to repair worn parts. The burning of the fuel gives rise to heat and also generates the work which it is the object of the engine to accomplish. Food in relation to the body fulfils the same two uses, for it undergoes combustion and thus the bodily heat is kept up, and work is rendered possible. Food also achieves the second function, and supplies the material for the repair of the body's framework which undergoes wear and tear as a result of activity. Here, however, the body is superior to the engine; in the case of the latter, repair has to be accomplished by means of "spare parts," or at any rate of material similar to those originally employed in the construction of the machine; the living body is able to utilise for repair certain materials, the proteins, etc., in the food which are not identical with its own substance, but which are rendered identical by digestive and metabolic processes.

The Requirement of Protein.

How much protein is really necessary in the diet is a subject which has been much discussed and which is of considerable importance, since this constituent of the diet when taken as meat is much more expensive than the others and there is evidence that excess may be harmful in that it may throw unnecessary strain on the organs which have to deal with it.

When we take in protein we do so essentially to replace tissue wastage which is indicated theoretically by the nitrogen excreted when no nitrogen is taken in the food; we must consider whether or not the minimum intake of nitrogen to replace nitrogen lost is really the optimum. As we shall see, the form in which the nitrogen is taken is of great importance.

By far the most important experiments on this subject are those of Chittenden on himself, his colleagues, and his students at Yale University, and on soldiers and athletes, over comparatively long periods of time. The protein intake was reduced to less than half the quantity hitherto regarded as necessary. There were no untoward results; indeed, it was stated that the muscular force in an athlete was increased. Mental activity was claimed to be undiminished, and the desire for rich food soon disappeared.

The important character of Chittenden's work gave the faddists on matters of diet an important opportunity of being listened to. There was, for instance, a group of these to whom the very necessary

act of chewing assumed almost the nature of a religious ceremony, and they have sought to convince mankind of its superlative importance.

There are in connection with the Chittenden diet several circumstances that should make us pause before we accept his conclusions to the full. Many people eat too much; would it be advisable for us all to eat too little, and is Chittenden's diet too scanty?

No doubt the over-eaters would benefit by eating too little for a time. They would give their overtaxed digestive and secretory organs a necessary rest, and have time to consume some of their accumulated stores of material. It is quite possible that the benefit noticed in some of the subjects of Chittenden's experiments was due to such a circumstance as this, or to the regular life they were compelled to live, quite apart from diet altogether. But to eat too little as an ordinary and permanent thing is quite another matter; and it is interesting to be able to record that most, if not all, of the subjects of Chittenden's experiments returned to their previous dietetic habits.

So far as it is possible to read history correctly, man has always, where he can, taken instinctively more protein than Chittenden would allow him, and with few exceptions, the meat-eating nations are those which have risen to the top.

If one may draw correct deductions on questions of diet from animals, a restricted diet over a long period proves detrimental. Moreover, a careful study of Chittenden's own analytical figures, such as Benedict has made, shows there was in some cases distinct impairment of health.

But still the question remains, why an apparently large excess of nitrogen which the body casts out within a few hours should be advisable? The answer to this appears to be, that though most of the cleavage products of protein metabolism are dealt with in this way, there are some which are especially precious for tissue reconstruction, and it is for these that we put up with the excess of waste. The large size and activity of the normal liver seem to be for the express purpose of dealing with this waste rapidly.

Nature does not work in minimums; Leathes puts it very well when he says it is not considered unphysiological to take more food than will yield the minimum of faecal refuse; and he also points out that in the infant, even allowing for its growth, the normal amount of milk provided for it by nature is ten times greater than would appear to be the necessary minimum; and this is probably a safer argument than the one so often used when the instinctive habits of past centuries of adults are appealed to. The Health Organisation of the League of Nations adopted a standard of 75 grams for the

average man of 70 kilos and slightly less for women, but in actual practice it may be said that there is so much protein in the natural foods that if sufficient calories are taken the protein intake will be adequate. Even the articles richest in carbohydrate, such as flour and potatoes, contain considerable quantities of protein, but it must be realised that these are not really natural foods, but have been specially developed to produce a large carbohydrate yield.

It is probable that young growing animals have a larger protein requirement than adults. It is usually considered that adults require about half that of an infant on milk; indeed this is clearly shown by a study of the amino-acids necessary for growth and for maintenance (see Protein Utilisation and Synthesis).

It would seem, however, that there may be an optimum protein intake. Young rats have been found to live longer and to have higher body-weights if fed on this optimum (about 16 per cent.) than those given amounts above or below this (Slonaker).

As we shall see later in relation to the use of protein in the body the proteins are necessary not only for repair but contain the amino-acids from which the body manufactures some of its most important regulators such as thyroxine, adrenaline, and insulin. The possession of such substances in abundance must contribute materially to the well-being of the individual and may assist him also in repelling bacterial invasion. It has been suggested that such undefined qualities as "energy" and stamina, in part at least, may depend on proteins, but the psychological make-up of the individual is probably as much concerned. The subject is dealt with in more detail in relation to protein synthesis.

The Specific Dynamic Action of Protein.—Protein has one property out of all proportion to that possessed by other foodstuffs: it very largely increases the production of heat in the body. People (as in Chittenden's experiments) on a low protein diet suffer intensely from the cold. One can double the heat production in a dog by giving it a large quantity of meat. The extra heat appears to be due to the deamination of amino-acids and the formation of urea (Wilhelmj). Experiments with glycine and other amino-acids have proved this fully. Protein acts then as a chemical stimulus to metabolism, and not in virtue of its energy-content. This *specific dynamic action* of protein must not be lost sight of in settling the right amount which we should take in our daily food. Roughly speaking, all the calories liberated in carbohydrate combustion may be used to produce work: the figure in fat combustion is nearly but not quite so high, while only about 70 per cent. of the protein calories are capable of conversion into any form of energy other than heat. As we have already observed, the specific dynamic action

of protein may vary in different individuals. A small increase of metabolism is produced when glucose is utilised (fig. 143).

Sources of Protein.—The main source of protein is the flesh of animals and fishes, but we can also get protein in milk, cheese, egg, potato, and even flour contains about 10 per cent.; the leguminous foods, peas, beans, lentils, also contain large quantities. These useful vegetables contain as much protein as beef and mutton, and if *properly* cooked are almost as easily digested. Nevertheless some proteins are better adapted to animal nutrition than others; the most adaptable are those of animal origin; but there are some vegetable proteins which are nearly equal to them, and of these the protein of potato stands pre-eminent; but unfortunately the potato does not contain very much (see The Biological Value of Protein).

Meat is eaten because it forms a concentrated form of easily digestible protein, and protein is the great repairer of tissue waste. As a source of energy, it is about equal to carbohydrate and far inferior to fat; considering its price its use is therefore not economical. The man who works hard physically requires little more meat than the man in the arm-chair. The "Roast Beef of Old England" is really not the source of a large amount of energy, however much the contrary may be believed by those ignorant of physiological principles. An engine called upon to do more work does not necessarily want repair: what it needs is more fuel (coal or petrol). The human engine, if healthy, is the same; the invalids who *do* need repair are dealt with on different lines. It must be admitted, however, that meat, especially if fatty, delays the onset of hunger longer than carbohydrate. This is often confusing to those who have not the required knowledge (see Hunger).

The war-time allowance of meat is quite sufficient for physiological purposes, and the reduction is of great benefit to those who had been big meat-eaters previously. The difference between meats lies largely in their palatability and their digestibility, *i.e.*, the readiness with which the digestive juices can penetrate between their muscle-fibres. The white flesh of chicken and fish of "light diet" is considered to be more readily digestible and hence it is given in illness when digestion is impaired. From our knowledge of digestion we know, however, that the cooking is often quite as important as the choice of the article in promoting digestion.

Many of the cheaper cuts of meat properly cooked and the flesh of the cheaper fishes such as herring and cod, or cheese are, as satisfactory sources of protein, not inferior to more expensive varieties. Fish is more expensive from this point of view than meat since it contains a smaller proportion of protein and more water. Freezing does not affect the nutritive value of food, but if flavour

is to be retained slow thawing is essential. There is, however, little accurate knowledge on the subject of flavour.

Vegetarian Diet.—The facts regarding the constitution of proteins, in spite of the pleadings of vegetarians, go most emphatically to show that vegetable proteins are not so valuable as animal proteins, which contain more adequate amounts of the essential amino-acids—a consideration which is specially important in the young. We shall also see later that the nitrogen requirement of the body is more readily supplied by meat, eggs, and milk than by any other source of protein. Moreover, as we have already noted, vegetable proteins are as a rule less digestible than those of animal origin.

The Daily Calorie Requirement will depend on the size of the man, on the temperature to which he is exposed, but chiefly on variations in his physical activities, as is indicated by the study of the average metabolic rates of persons employed at different occupations. This has already been discussed in the previous chapter. A man of average size who stays in bed for the twenty-four hours needs about 1700 large calories in the day to maintain his temperature and his respiration, to keep his heart beating, and so forth. The remainder of the calorie supply in an active person can be utilised for the performance of work. The peace-time allowance for a man doing a day's moderate muscular labour is food equivalent to about 3400 calories, and under condition of extreme work this may rise to 4000 in a day or even higher.

The British civilian ration during war is below the 3000 level for those not engaged in severe physical work. At such a time the civilian population has to put up with such a trivial hardship in order that active workers (munitioners, labourers, and men at the front) might get the share they really needed. Those who are engaged on particularly hard physical work, *e.g.* woodcutters, requiring 5000 to 10,000 calories, are unable to take all the calories they need in the form of carbohydrate and have to be given a special ration of fat in spite of the shortage of that commodity which is used for making munitions. The extra is conveniently supplied as fat bacon, and fat, as we have seen, is a condensed form of fuel, and it is this which is so necessary for stoking up the furnace when extra expenditure of energy is needed.

In making calculations for large scale investigations, the system of man-values introduced by Cathcart and Murray is commonly used in which a man is considered as needing 1·00, *i.e.* 3000 C., a woman 0·83, and children under three as 0·40, 0·10 being added for each two years until adult value is reached—at 14 years. Persons over 65 years are calculated as 0·75.

Rations for Brain-workers.—The brain works economically:

any measurable increase in energy-output is negligible, and so it may be at once said that the brain-worker requires no increased intake of food. The food must naturally be easily digestible; one cannot expect a man to do good mental work who is suffering from the pangs of dyspepsia, but beyond this anything further is unnecessary.

The subject of the storage and loss of calories has been discussed further in the section on Body-Weight.

The Balance of the Diet.—As has been stated in the previous chapter, each food constituent has a definite calorific value per gram: protein (in the body) 4.1, carbohydrate 4.1, and fat 9.3, but the relative amounts of each which may be taken depend largely on personal taste and on the actual articles of diet available.

The various diets put forward by older investigators have much in common with those which have been officially recommended of recent years.

It is considered that the figure 3400 calories should be made up from 100 grams of protein, of which 50 grams should be protein of animal origin, 100 grams of fat, preferably of animal origin, 400 grams of carbohydrate. (Ministry of Health Committee.)

The actual amount of carbohydrate may, however, be greatly increased according to the amount of physical work done. This allows for 10 to 15 per cent. of the daily calorific requirements to be derived from protein and for any waste due to incomplete digestion and in preparation. Such a diet supplies more calories than the older diets of Voit or Ranke, which were, however, sufficient for sedentary occupations. Attention must also be paid to salt and vitamin requirements. An idea of what, under modern conditions, appears to be the best choice of diet from the point of view of cost and efficiency is indicated by the tables given at the end of this chapter.

The physical characteristics of food affect the amount which can be taken. For example, it would be theoretically possible to supply all the calories in the form of meat, but it would require some six pounds, and clearly the quantity would become unpalatable. Fat is essential when large amounts of physical work are being done. If this constituent of the food is reduced, disagreeably large quantities of the other foods have to be taken to make up the required calories.

Official Dietaries.

Those who are responsible for the health of the nation have experienced very great difficulty in educating those whose finances

are limited in the choice of an efficient diet, for custom dies hard and it is difficult to obtain realisation of the fact that cost, palatability, and efficiency are by no means parallel. The following tables, published by the British Medical Association, will act as a guide to those living on the ordinary mixed diet of temperate climates. They are designed to supply all the requirements set out in the above chapter. The prices for meat are those for imported foreign products in 1936. The cost does not, of course, include that of cooking.

Individual Weekly Diets.

Diet No. 1.—Bare ration. No variety. Man-value, 1.

Item.	Quantity.	Price (1936).	Protein (grams).	Fat (grams).	Carbo- hydrate (grams).	Calories.
Corned beef . .	1 lb.	s. d. 0 6	119.2	84.8	...	1,278
Cheese . .	2 lb.	1 1	233.2	317.6	28.2	4,022
Margarine . .	$\frac{3}{4}$ lb.	0 3	0.7	288.5	...	2,684
Flour, or . .	7 lb.	...	320.6	51.1	2397.5	11,620
Bread . .	11 $\frac{1}{4}$ lb.	1 7 $\frac{3}{4}$	(367.9)	(10.1)	(2454.8)	(11,666)
Sugar . .	1 $\frac{3}{4}$ lb.	0 4	793.8	3,255
Potatoes . .	3 $\frac{1}{2}$ lb.	0 2 $\frac{1}{2}$	30.1	0.4	287.4	1,306
Tea . .	$\frac{1}{4}$ lb.	0 3
Fresh fruit and green vegetables	...	0 7	100
Total weekly quantities	...	4 10 $\frac{1}{4}$	703.8	742.4	3506.9	24,265
Daily quantities per man	100.5	106.1	501.0	3,466

Total first-class protein, 352.4 grams.

Daily first-class protein, 50.3 „

Cost per man per week, 58.25 pence.

NOTES.—Diet No. 1.

Diet No. 1 gives quantities of protein, fat and carbohydrate, and of total calories adequate to support working capacity. This diet, although adequate in its principal constituents, may be deficient in vitamins and minerals, but the principal defect lies in the small number of its constituent foodstuffs. Though perhaps palatable for a period of one week, it would with longer use rapidly become monotonous and nauseous. In order to avoid the repugnance which would inevitably follow the prolonged ingestion of such a diet, and to assure adequacy of vitamins and minerals, it is necessary to increase the number of foodstuffs so as to obtain greater variety.

Diet No. 2.—Suggested adult ration, based on 50 grams. First-class Protein. Giving 1/4 pint milk. Man-value, 1.

Item.	Quantity.	Price (1936).	Protein (grams).	Fat (grams).	Carbo- hydrate (grams).	Calories.
Beef	1 lb.	s. 0 d. 6	85·3	83·5	...	1,126
Minced meat	1/2 lb.	0 2 1/2	42·7	41·8	...	563
Bacon	1/2 lb.	0 3	23·3	122·9	...	1,239
Corned beef	1/2 lb.	0 3	59·6	42·4	...	639
Liver (Ox)	1/4 lb.	0 1 3/4	22·6	3·6	5·0	147
Eggs	2 oz.	0 1	6·3	5·7	0·8	82
Cheese	1/2 lb.	0 3 1/4	58·3	79·4	7·0	1,005
Milk	1 3/4 pts.	0 5	32·7	35·7	47·6	661
Fish (Cod)	1/4 lb.	0 1 1/4	16·6	0·1	...	69
Butter	1/4 lb.	0 2 1/2	0·2	94·1	...	876
Suet	1 oz.	0 0 1/4	0·3	26·4	...	247
Lard	1/4 lb.	0 1 1/2	...	113·4	...	1,055
Flour or	4 1/2 lb.	...	206·1	32·8	1541·2	7,470
Bread	7 1/4 lb.	1 0 1/2	(237·0)	(6·5)	(1581·9)	(7,518)
Sugar	1 lb.	0 2 1/4	453·6	1,860
Jam	3/4 lb.	0 3 1/4	1·1	...	236·1	972
Potatoes	5 lb.	0 3 3/4	43·0	0·5	410·5	1,865
Peas (dried)	1/4 lb.	0 1	23·1	0·7	64·7	367
Tea	1/4 lb.	0 3
Oatmeal	1/2 lb.	0 1 1/4	27·0	19·5	158·7	943
Rice	1/4 lb.	0 0 3/4	6·7	0·5	91·1	405
Syrup (treacle)	1/2 lb.	0 2	0·7	...	173·3	714
Cabbage	1 lb.	0 1	3·2	0·2	17·7	88
Beans (butter)	1/4 lb.	0 0 3/4	21·1	0·8	70·5	383
Barley	1/2 lb.	0 1	15·8	1·8	181·2	825
Fresh fruit and green vegetables	...	0 7	100
Total weekly quantities	...	5 10 1/2	695·7	765·8	3439·0	23,701
Daily quantities per man	99·4	100·8	491·1	3,386

Total first-class protein, 347·6 grams.

Daily first-class protein, 49·7 „

Cost per man per week, 70·5 pence.

It should be pointed out that the prices given are those for foreign imported produce, which is not generally available in all parts, but at the same time it must be remembered that many of the more expensive portions of an animal are not any more nutritious than the cheaper cuts.

Typical Meals.

The following are typical diets, kindly supplied by R. D. Lawrence, of students in residence at a university hostel.

Case A, aged 25; height, 5 ft. 11 in.; weight, 11 st. 4 lb. (71.6 km.). Average weight for height is 10 st. 13 lb., so that he is slightly above weight; habits not active except that he usually bicycles about 10 miles a day; noticeably a big eater.

Food.	Weight in Ounces.	Food Content in Grams.		
		C.	P.	F.
<i>Breakfast</i>				
Porridge	10½	35	7	7
Sugar	1	30	0	0
Kipper	1½	0	8	3
Butter	1	0	0	25
Toast	2½	45	4	0
Marmalade	1½	27	0	0
Milk	3	5	4	4
		142	23	39
<i>Lunch</i>				
Roll, bread	1	15	3	0
Sausage	1½	1	5	12
Potato	4	27	3	0
2 Apples	10	32	1	1
		75	12	13
<i>Tea</i>				
2 Biscuits	1	20	4	0
Milk	2	3	2	2
		23	6	2
<i>Dinner</i>				
Soup, thick	3½	6	3	2
Steak }	7	0	52	26
Pudding }	2½	28	3	3
Onions	8½	11	2	3
Potato	7½	50	5	0
Bread	1	15	3	3
Stewed fruit	4	15	2	0
Custard	2½	17	4	4
Sugar	½	15	0	0
		157	74	41
<i>Supper</i>				
Treacle cake	6	120	3	10
Total for day		517	118	105
Calories		2068	472	945

Total = 3,485.

Weight = 71.6 kgm.

Calories = 48.7 calories per kgm. of body weight.

Case B, aged 35; height, 5 ft. 2½ in.; weight, 9 st. 10 lb. (61·6 kgm.). Average weight for height is 8 st. 8 lb., so that he is above the average weight and is noticeably obese; active and quick in his movements, but takes no exercise, not even walking; noticeably a small eater; has a distaste for fat and butter; probably partly restricts his food to avoid obesity.

Food.	Weight in Ounces.	Food Content in Grams.		
		C.	P.	F.
<i>Breakfast</i>				
Bacon, lean	$\frac{1}{2}$	0	5	5
Potato	1	6	1	0
Toast	$\frac{3}{4}$	15	3	0
Marmalade	1	25	0	0
		46	9	5
<i>Lunch</i>				
2 Crumpets	2	30	6	0
Butter, 2 pats	$\frac{1}{2}$	0	0	12
Mince pie	—	20	4	5
Jam tartlet	—	25	4	0
		75	14	17
<i>Tea</i>				
2 Rock cakes	$1\frac{1}{2}$	22	4	4
<i>Dinner</i>				
Soup, thick	$3\frac{1}{4}$	6	3	2
Steak }	3	0	22	11
Pudding }	$1\frac{1}{2}$	17	2	2
Onions	$4\frac{1}{4}$	6	1	2
Stewed fruit	$7\frac{1}{2}$	28	3	0
		57	31	17
<i>Supper</i>				
2 Biscuits	1	20	4	2
Total for day		220	62	45
Calories		880	248	405

Total Calories = 1533.

Weight = 61·6 kgm.

= 24·8 calories per kgm. of body weight.

If we calculate his calorific usage on the average weight, which is more correct in some ways, as his "extra" fat is not metabolically active tissue, then we get the figure of 29 cal. per kgm. of body weight.

Case C, aged 24.; height, 5 ft. 11 in.; weight, 9 st. 4 lb. (59 kgm.). Average weight for height is 10 st. 13 lb., so that he is considerably under weight and is quite thin; he is active and plays games occasionally, but not daily; eats slightly less than the average student.

Food.	Weight in Ounces.	Food Content in Grams.		
		C.	P.	F.
<i>Breakfast</i>				
Porridge	5	16	3	3
Milk	5	7	5	5
Sugar	$\frac{1}{2}$	15	0	0
Bacon	$\frac{1}{2}$	0	3	8
Potato, fried	$2\frac{3}{4}$	20	2	5
Toast	1	20	4	0
Butter	$\frac{1}{4}$	0	0	6
Marmalade	$\frac{1}{4}$	19	0	0
		97	17	27
<i>Lunch</i>				
1 Sausage	—	1	5	12
Potato	6	40	4	0
Brussels sprouts	4	4	2	0
1 Slice jam roll	—	25	1	0
		70	12	12
<i>Tea</i>				
1 Banbury cake	—	20	4	0
Milk	$\frac{1}{2}$	1	0	0
		21	4	0
<i>Dinner</i>				
Soup, thick	$5\frac{1}{4}$	8	4	3
Steak }	3	0	22	11
Pudding }	1	12	1	1
Potato	3	20	2	0
Onions	2	3	0	1
Stewed fruit	4	15	2	0
Custard	$1\frac{1}{2}$	10	3	3
Milk	$3\frac{1}{2}$	5	3	3
		73	37	22
Total for day		261	70	61
Calories		1044	280	549

Total Calories = 1873.

Weight = 59 kgm.

= 31.7 calories per kgm. of body weight.

The Salt Requirement.

Until comparatively recently the salts in the diet were ignored and patients suffering from various conditions were often treated with medicines which did little to remedy dietetic deficiencies, but it is now recognised that long before people are taken ill their activity may be impaired by prolonged deficiency in salts. In regard to diet generally and to salts in particular, it is pointed out that a given article of diet, particularly of a vegetable nature, is not always of the same composition. This depends to a very considerable extent on the soil in which the vegetable is grown. Unfortunately the public have not learnt to recognise salt-deficient vegetables in so far as this is possible.

But the presence of the salts in the diet does not necessarily mean they are absorbed into the blood stream. This may be interfered with by the presence of other substances in the diet; for example, excessive calcium reduces the absorption of iodine. Sometimes, too, conditions are present in the intestine which upset absorption. This is common both in relation to iron and iodine.

There seems to be little doubt that some benefits attributed to "change of air" are attributable to change of mineral intake.

Sodium and **Potassium** are essential in the diet but are so well distributed in nature that a dietetic deficiency in respect to them is unlikely.

Calcium.—It is being recognised that as different parts of the country vary considerably in their supplies of this element, this may be of dietetic importance. Some areas are deficient while in others there is an excess which may interfere with the absorption and use of other elements. Its importance to the body is indicated by the fact that it is one of the substances which is maintained at a constant level in the blood by mechanisms which are described in a later section. The daily excretion of a fasting man is about 0.5 gram, but double is usually considered desirable in the diet and more is needed during pregnancy and lactation when acute symptoms of calcium deficiency commonly occur in women and domestic animals, notably cows and cats. According to Campbell, Bessey, and Sherman, who experimented on rats, calcium deficiency may show itself in a second generation rather than the first. Young animals deprived of calcium do not grow so well or so rapidly and it is stated that they do not live so long as those adequately supplied. The workers in Columbia University have emphasised the importance of calcium in promoting the general vitality of their animals.

At the same time it should not be overlooked that there may be some adaptation to low calcium diets. Some plants we know, such as *primulæ*, thrive best on calcium deficient soils while others,

such as rock roses, grow best where chalk is abundant. It is possible that there may be similar differences, hereditary or acquired, in the human subject.

Calcium is provided by meat and all the usual vegetables (averaging from 0.01 to 0.3 per cent.) in small amounts, but milk contains about 0.12 per cent., while in cheese this is concentrated more than fourfold. Even when there is sufficient in the diet, only a small proportion is absorbed, 20 to 50 per cent. in adults but more by children. When excess is absorbed it is excreted in the urine. There is some discussion as to whether the calcium found in the faeces is an excretion or is calcium that has not been absorbed. Evidence now favours the latter view.

A moderately hard water, such as this of London, contains about 0.03 per cent. of calcium, but of that more than two-thirds is temporary hardness, that is, soluble bicarbonates which are precipitated when the carbon dioxide is driven off by boiling.

The *absorption of calcium* has been a subject of considerable discussion, for calcium is readily precipitated as phosphate in alkaline solution but it is soluble in acid solution. Certainly the administration of hydrochloric acid facilitates the absorption, and sodium bicarbonate hinders it, but how far the small intestine is acid is very problematical for the bile and pancreatic juice are alkaline. There is now increasing evidence that bile salts, amino-acids, and fats may facilitate the absorption by a hydrotropic action and also vitamin D. The whole subject is, however, one of great complexity and cannot be looked upon as settled, but it is of great importance in relation to the growth of the bones and teeth.

The Functions of Calcium are dealt with later.

Phosphorus.—As we shall see in a later section phosphorus is necessary for a large number of body processes. A phosphorus equilibrium is maintained by the action of the parathyroid glands, that is, the excretion is balanced by an intake of about 0.8 gramme per day, but probably appreciably more is needed in the optimum diet, especially when the foetus or young animal is growing, for calcium is laid down in the bones as phosphate. Of the common foods milk and milk products contain most and thereafter wheat and oats. It is present in phosphoproteins such as the caseinogen of milk and the vitellin of eggs, in the lecithin of eggs, liver and blood, and in the nucleic acid of all cell nuclei. Inorganic phosphates occur chiefly in meat and milk and plants. Much of the phosphorus of plants—phytin phosphorus—is not digested or utilised. In some regions the phosphorus of the soil is poor, and in South Africa the nutrition of the cattle is thereby affected.

The Functions of Phosphorus are dealt with later.

Iron.—It has long been known that iron was necessary for the body and it has been regularly used in so-called “tonics,” but it was not realised till recently that deficiencies in the diet were of such importance.

Iron is needed for the formation of almost all tissues, but by far its most important use is in the formation of the hæmoglobin of the blood and the cytochrome of the tissues which are concerned with the carriage of oxygen and its use in the tissues respectively. It has been claimed to be concerned in almost all enzyme systems in the body and also to be present especially in the nutrition of epithelial surfaces, since deficiency may be associated with cracking of the skin and lips. It is, however, in the anæmias that iron deficiency is most commonly evident.

Deficiencies in this element have long been recognised as a cause of a simple anæmia characterised by insufficient hæmoglobin in the blood. The disease was particularly common amongst women prior to about 1910, but lesser degrees are still common, women being thought particularly subject because of their monthly loss of blood during menstruation. Even fasting men, however, excrete from 7 to 12 mg. per day by the bowel, and the menstrual loss of 3 mg. adds but little to the daily average. During pregnancy the need for additional iron in the diet is obvious for much is needed for the formation of hæmoglobin in the foetus. The supply at this stage is specially important, since milk contains so little and young children are therefore specially liable to suffer from anæmia. The extent to which it is absorbed from the intestine normally appears to be dependent on the hæmoglobin content of the blood. Iron is probably absorbed as ferrous salts. Blood and chlorophyll are of no value as a source of iron in the diet as the iron cannot be liberated by the body.

When the red blood-corpuscles die after their normal month or so the iron set free is taken up by the reticulo-endothelial system and is stored as the pigment hæmosiderin especially in the liver, kidney, and spleen. It is especially abundant in these sites when there is excessive breakdown of corpuscles or inadequate utilisation of the iron.

Excretion of iron occurs in the large intestine, but most of the iron in the fæces has never been absorbed. The body holds on somewhat tenaciously to what it takes into the blood stream.

It is suggested that 0.4-0.5 mg. of iron per 100 calories of diet is desirable for the general population (Rose).

Most articles of diet contain iron, but the following are the most important, the numbers following indicating the approximate amounts in milligrams, given by Sherman, per 100 grams: beans (10), dried peas (5.7), wholemeal flour (5), oatmeal (4.8), eggs (3), lean

beef (3), cheese (1·3), milk (0·24), spinach (2·5), kale (2·5), potatoes (1), beet (0·8), turnips (0·5), carrots (0·6), tomatoes (0·44) other vegetables and fruits less. It is of interest that wholemeal flour loses four-fifths of its iron when it is refined to white flour. Workers in this field emphasise that vegetables and fruit offer the easiest method of supplying iron to the body without increasing the calorific value of the diet, even allowing for the fact that not all the iron in vegetables is used.

Copper.—So far as can be ascertained traces of copper are an advantage in the formation of hæmoglobin. In crustaceans the normal green blood pigment, hæmocyanin, contains copper instead of iron. It is found in minute quantities in a number of vegetables, especially lettuce, and fruits, especially currants; it is also present in cocoa, corn, nuts, wheat, bran, and legumes. Liver seems to be richest in this element possibly because it is stored in this organ. Only very minute amounts are needed in the diet.

Iodine is necessary for the formation of thyroxine, the very active substance elaborated by the thyroid gland which we have seen is so important in regulating the metabolic rate. Many regions of the world have iodine deficient soils and this affects the iodine content of its plants. Normally we get our required iodine, which is only about 0·00014 gram daily (Fellenberg), in milk, sea-fish, oats, potatoes, carrots, eggs, and onions, but in goitrous districts it is necessary to add iodine to the table salt. Infants need more than adults.

Magnesium.—This element is a constituent of the chlorophyll of plants and is very closely associated with calcium in the skeletons of animals, although it is present in minute quantities in practically all tissues and body fluids. In the urine it is found in association with phosphates, normally as MgHPO_4 and abnormally in ammoniacal urine as NH_4MgPO_4 . Like calcium it antagonises potassium physiologically. It has been found that if it is completely absent from the diet of rats and dogs they die in convulsions. It seems probable that death is due to a failure of the acid phosphatase enzymes of the body or the glycogen break-down system for the action of which magnesium appears to be necessary.

Fluorine is also present in minute quantities in plants and is considered to contribute to the hardness of the skeleton and especially of the enamel of the teeth. Large amounts in the diet produce the opposite effects.

Manganese is present in a large variety of vegetables in minute quantities. Various claims have been made that it is essential for normal reproduction and it is always present in developing eggs and in the reproductive organs.

Water.

Water is necessary for the solution of the foodstuffs prior to absorption in the blood stream, and innumerable functions in the body. The subject is discussed later in relation to Water Balance.

Vitamins.*

Although a diet may be adequate from the point of view of protein, carbohydrate and fat, it has now been definitely established that certain accessory food substances are necessary in the diet to

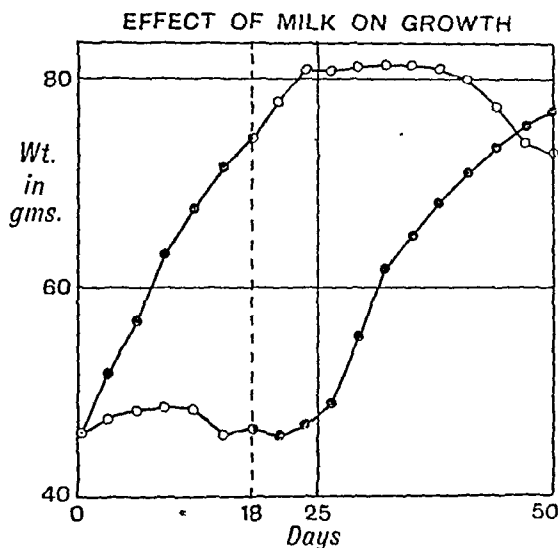


FIG. 144.—Curves of growth of two sets of rats. That shown in dark dots received for the first eighteen days 3 c.c. of milk daily in addition to a diet of casein, lactose, and salts. At the nineteenth day the milk was omitted. The other set had the same diet but no milk for the first eighteen days. Thereafter they were given 3 c.c. of milk daily. (From the original of Hopkins.)

maintain good health, especially of growing animals. Experience gained in expeditions, in the old sailing ship days, and of the health of prisoners, had long indicated that mere calories and proteins were insufficient to sustain life, but it was not, however, until Hopkins of Cambridge, in 1912, from his investigation of restricted diets in relation to the essential amino-acids, placed the subject on an experimental basis that the importance of these accessory food factors was fully appreciated, although admittedly much uncorrelated and not generally recognised clinical evidence, notably that of Eijkman, in 1890 (see below), was available.

The factors are; for the most part, products of the plant world, and from this source they are acquired by animals. Many are relatively simple chemical substances and have now been obtained in a crystalline form. They may be distinguished by differences in

* So called because they were thought originally to be amines.

their source, in their action and in the maladies (deficiency diseases) which result from their absence. In addition to those described below there are, however, many other substances which are necessary for the health of lower animals and the growth of bacteria. Only those important to man are discussed.

The Fat-Soluble Vitamin A.—In 1912 Hopkins fed young rats on pure food mixtures containing approximately the constituents of milk, viz: caseinogen, fat, starch, cane-sugar, and inorganic salts. The energy-value was adequate but growth ceased. His famous growth curves are shown in fig. 144. The addition of a minute amount of fresh milk caused the recommencement of growth. In 1881 Bunge had come to a similar conclusion from work on mice. In 1913 McCollum and Davis showed that this essential substance for growth, both vitamins A and D, was present in the fats of butter and egg yolk. There was at first confusion between the fat soluble vitamins, but it is now known that Hopkins's rats did not grow because of deficiency of vitamin D as well as vitamin A. Their sources are, however, very similar. The original source is the pro-vitamin A of the green plant, whence it is acquired by animals, and becomes dissolved in their fat. Thus it is present in milk and butter, provided the cows are fed on green food. Animals have the power of storing the vitamin in their livers from which it may be obtained in the oil. The oils of fishes which feed on green plant organisms in the sea, either directly or by eating smaller fishes which do so, are particularly rich in the vitamin. Hence the virtue of fish liver oils. Butter substitutes, such as margarines made from vegetable fats, have usually no vitamin A and little D.* Both A and D are present in egg yolk.

Properties.—It is important to observe that vitamin A is very liable to destruction on heating, but it is now clear that this depends on oxidation processes. Milk can, therefore, be sterilised at quite high temperatures in an autoclave (air free) without losing vitamin A, which, however, is destroyed by ordinary boiling or even free aeration at all temperatures. Speaking generally, condensed milk still has enough vitamin A, and dried milk also, provided the latter has been made by a process such as passing it over a heated drum, which dries without permitting too long exposure.

Deficiency in vitamin A leads to the lack of growth of young animals, which is eventually fatal.

Action.—Vitamin A appears to provide the necessary stimulus for the building of new cells. This failure of cells to grow is well seen in the epithelial coverings of the body which tend to become dry and keratinised. This occurs in the conjunctiva of the eye, in the respiratory tract, and especially in the vagina. The hair also

* In war-time vitamin D has been specially added in Britain.

becomes dry and lustreless. The lack of vitality in these regions leads to a liability to infection which is marked in the eyes, where it is accentuated by deficient secretion from the lachrymal glands (tears). Degeneration of the spinal cord and interference with reproduction may also occur. Deficiency also leads to night blindness from interference with the formation of the visual purple.

Chemistry.—The parallelism between the yellow colour and potency of vitamin A in foods (Steenbock) led to the finding that the vitamin is related to the pigment carotene. It has been shown that the administration of carotene causes the characteristic blue colour with antimony trichloride to appear in the livers and prevents signs of deficiency in rats fed on a diet deficient in vitamin A. The results suggest that *carotene* is converted into the vitamin in the liver. There are in nature a number of pro-vitamins A or carotinoids which have themselves been synthesised in plants from precursors by the influence of light, but these appear to be only of value to man as precursors. Vitamin A is an unsaturated alcohol having the formula $C_{20}H_{30}O$. Its strong absorption band in the ultra-violet is characteristic and is made use of in estimations. On oxidation it becomes converted into a derivative of carotene known as geronic acid.

The vitamin A standard is the vitamin activity of 0.6 microgram of a standard preparation of β -carotene and about four times this will prevent signs of deficiency in rats on a diet deficient in this vitamin.

The vitamin is stored, especially in the livers of animals, a fact which no doubt does much to counteract the effect of any temporary reduction in the diet. It is also found in the testis, ovary, and adrenal cortex, a fact which may be of importance in regard to reproduction.

A vitamin A which differs in its absorption spectrum has been differentiated, but its action appears to be similar.

The Antirachitic or Calcifying Vitamin D, and Sunlight.—

In the study of animals fed on diets deficient in vitamin A it was found that rickets was commonly produced, and later it was recognised that the antirachitic and growth-promoting vitamins were present in different amounts in fats from different sources.

Source.—This vitamin has the same source as vitamin A, but may be distinguished from the latter by the fact that it is less easily oxidised; for example, cod-liver oil if exposed to the action of ultra-violet light or of oxygen at $100^{\circ}C$. for twenty-eight hours loses its power to cure xerophthalmia in rats while the action of vitamin D remains (McCollum). It therefore withstands ordinary cooking and preserving better than A. Butter, on the other hand, is less active than cod-liver oil in curing rickets, although more

effective in curing xerophthalmia. Vitamin A may also be distinguished by the fact that it gives a blue colour with antimony chloride. Vitamin D is present in small quantities in vegetable oils which contain no vitamin A. Tunny fish-liver oil contains most. This vitamin is present in yeast and a wide range of lower plants when fresh, but they rapidly lose their vitamin when cut. As in the case of A, ordinary winter milk, therefore, contains very

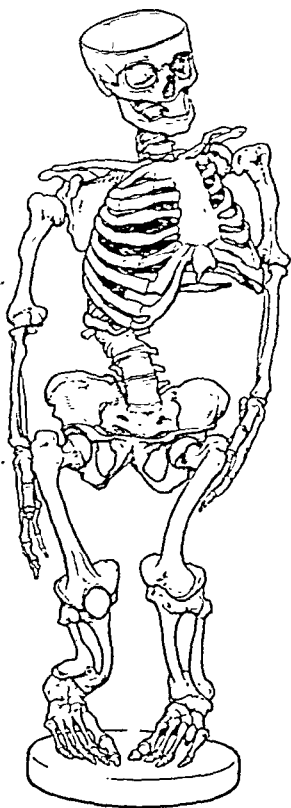


FIG. 145.—Rickets in man. (Drawn from a photograph by J. C. Brash of the skeleton of Bowed Joseph in the Anatomical Museum in the University of Edinburgh.)

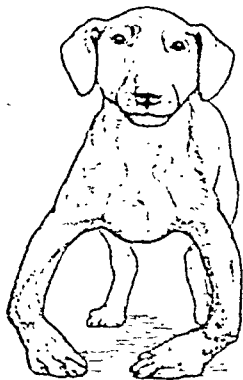
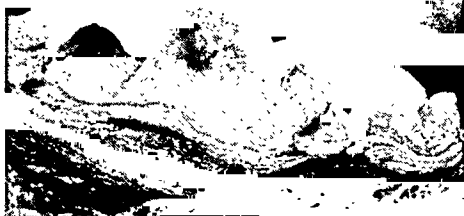


FIG. 146.—Rickets in a dog. (Drawn from a photograph by E. and M. Mellanby.)

little of the vitamin unless the cows have been specially fed on fresh green food.

Deficiency.—The absence of vitamin D or of sunlight leads to imperfect calcification of the bones (rickets) and of the teeth, and in this connection it may be noted that, in 1906, Hopkins suggested this possibility, which was subsequently confirmed experimentally on dogs by E. Mellanby, to be due to the absence of a fat soluble vitamin, although at that stage vitamin D had not been separated from A. In rickets the bones are so soft that

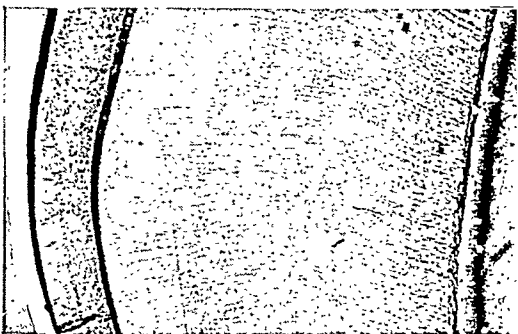
A
Basal diet only



B
+ Carotene



C
+ Vitamin D



D
+ Carotene
+ Vitamin D



FIG. 146A.—Photographs of the surface and photomicrographs of sections of the lower carnassials of four puppies of the same litter. The basal diet included oatmeal, peanut oil, separated milk powder, salt, yeast, lean meat and orange juice, and was the same for all.

A. Basal diet only. The enamel surface is rough and pigmented. Histologically the enamel is very thin and the dentine is also very thin and poorly calcified, showing many large interglobular spaces.

B. Carotene added to the basal diet. The enamel surface is rough and pigmented. Histologically the enamel is thin and slightly pigmented, while the dentine is thicker than in A but shows many interglobular spaces.

C. Radiostol added to the basal diet. The enamel surface is comparatively smooth and white. Histologically the enamel is thick and well calcified, while the dentine is very much thicker than in B and well calcified.

D. Carotene and radiostol added to the basal diet. The enamel surface is comparatively smooth and white. The section shows thick enamel and well calcified dentine. (Lady Mellanby.)

the legs bend under the weight of the body. Bow-legs, knock-knees, and many other deformities especially of the spine and pelvis may occur. The child is described as having "the head of a philosopher, the legs of a grand piano, and the belly of a poisoned pup." There is lowered phosphorus (1.5 mg. per 100 c.c. instead of 5 mg.) and calcium* in the blood. The bones of rachitic animals will calcify if incubated in normal serum, but not in rachitic serum, showing that the bone has the power to calcify if the salts are available. (See Hess, 1929.)

That lack of vitamin D produces dental caries has now been abundantly proved by Lady Mellanby, although, apparently, some persons require more vitamin D than others. There seems to be little doubt too that many children in receipt of a full quantity of vitamin D have caries because of their difficulty in digesting fat or other digestive disturbances. Attention to the diet and the giving of vitamin without the fat may result in striking improvement. For complete dental developments carotene appears to be also an advantage. See fig. 146A. (See Mellanby, 1928, and Marshall, 1924). It seems probable, however, that there may be still some unknown factors, possibly local conditions in the mouth, for rickets and caries are not necessarily both present in the same individual.

The function of the vitamin is, apparently, to correct any improper balance between the calcium and phosphorus intake, and the greater the disproportion of these two elements the more important the vitamin, but even if these substances are present in proper amounts the vitamin is necessary. The vitamin appears to increase the retention in the body of calcium which may be available in the food, probably by increasing the amount absorbed from the intestine.

Not long ago there were opposing views on rickets and its treatment. One group of workers insisted on the importance of diet (E. Mellanby and others), and another insisted on exercise and sunlight (L. Findlay, Paton). The discovery by Huldchinsky in 1919, that ultra-violet light would cure rickets and that vitamin D may be produced in foods by similar treatment, has shown that both were right. This production of the vitamin D_2 by irradiation depends on the presence of ergosterol (a sterol first obtained from ergot), but it has been found that 7-dehydro-cholesterol also becomes active when irradiated (D_3). In man, it is assumed that the sunlight activates ergosterol in the skin, for the feeding of excised human skin if irradiated will protect rats against rickets but not if not irradiated. How this occurs is not yet clear, since the penetrating power of ultra-violet light through skin is very poor, being only

* The calcium also falls, but later.

a millimetre Excess of the vitamin leads to excessive precipitation of calcium throughout the body especially in the arteries and kidneys (Kreitmar and Moll).

Chemistry.—A pure crystalline substance “calciferol,” which is a distillate of irradiated ergosterol which has all the properties of vitamin D, has now been prepared (Bourdillon) and found to be the isomer of ergosterol. The activity of 0.025 microgram of this has been adopted as the international unit.

There is increasing agreement that children should be supplied with 600-700 units daily and adults with about 200 units (Ministry of Health) associated with an adequate supply of calcium and phosphorus.

Vitamin D is antagonised by feeding animals on certain cereals, especially maize and oatmeal, which contain phytic acid. If, however, the oatmeal is cooked slowly the phytic acid is destroyed by a phytase normally present. Wholemeal bread is therefore rachitic but not porridge properly made and especially when taken with whole milk.

In conclusion it may be added that the making of a few dogs rickety has resulted in almost banishing from Britain a disease which, until comparatively recently, was responsible for the death or crippling of thousands of children. This is a fact worthy of contemplation by those who condemn animal experiments.

The Water-Soluble Antineuritic Vitamin B₁.—*Source.*—This vitamin is contained in the outer layer of all seeds, which layer contains the embryo plant, and may be removed in milling. It is therefore practically absent in white flours, but present in whole-meal flours. Since it is fairly resistant to heat, it survives ordinary baking, provided the temperature does not go above 100°C. The vitamin is also present in the yolk of eggs but not in the white, and milk and meat contain very little. Commercial preparations are made from yeast, a rich source of this vitamin, and also from rice polishings and bran.

Deficiency.—It was observed by Eijkmann* in Java, in 1890, that the use of polished rice led to the production of so-called polyneuritis, which caused paralysis both in man and in birds, although the diet was apparently otherwise adequate. The addition of the rice polishings, or of aqueous extracts of these to the diet, cured and prevented the condition.

The peripheral neuritis which results in paralysis or weakness of muscles and in anæsthesia, has led to the vitamin being known as the antineuritic one. This avitaminosis is characterised by general wasting and degeneration of tissues which are due to the inanition following a lack of appetite specific to the lack of vitamin B₁. In

* Eijkmann and Hopkins shared a Nobel Prize for their discoveries.

pigeons there is opisthotonos (dorsiflexion of the spinal column), convulsions from involvement of the brain—and death in about four days after complete lack. Both acute and chronic symptoms are known; unlike the former the latter do not clear up quickly when the vitamin is given. Reproduction is indirectly affected by oxygen lack.

In man the disease is known as beri-beri, in which there are commonly nerve degenerations due to a simultaneous vitamin-A deficiency which must be treated also (Strong and Crowell).

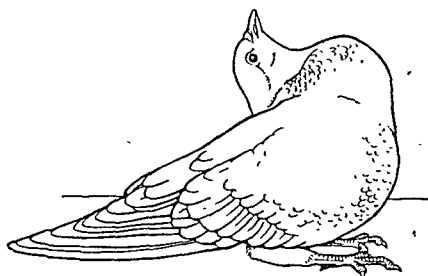


FIG. 147.—Pigeon suffering from vitamin B₁ deficiency.

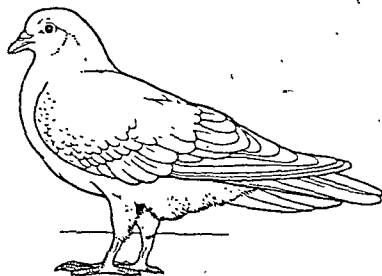


FIG. 148.—Same pigeon after the administration of the vitamin. (From M.R.C. Report.)

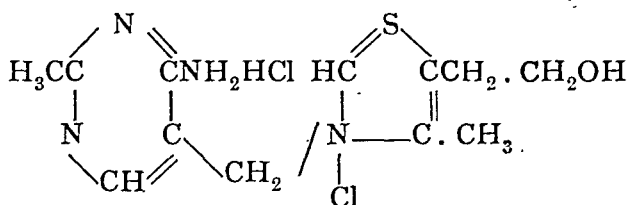
According to McCarrison, deficiency of this vitamin causes an increase in the size of the suprarenal and is responsible for much general malaise and lack of vigour in man. It is claimed also that deficiency in this vitamin results in a loss of tone of the gastrointestinal muscles.

Beri-beri was common amongst the rice-eating peoples and in 1880 afflicted more than one-third of the Japanese Navy; but in 1885 a change to a mixed European ration reduced the incidence to negligible proportions, although its exact cause was not recognised. Deficiency produces a hypertrophy of the adrenal cortex and a 50 per cent. reduction of the zinc content of the skin and nails. Some animals, such as sheep and cattle, appear to be able to synthesise the vitamin by means of their alimentary bacteria.

Chemistry.—Jansen, Windaus, Peters and others have succeeded in extracting from yeast crystals of a vitamin B₁ hydrochloride, C₁₂H₁₆ON₄S, 2HCl, of which 0.002 mg. per day protects pigeons against the neuritic symptoms. The crystals give a specific diazo-pink colour reaction (Kinnersley and Peters) and according to Williams have a pyrimidine-thiazole nucleus.* This is now known

* Its chemical name is 4-methyl-5-β-hydroxy-ethyl-N [(2 methyl-4 amino-pyrimidyl-5] methyl) thiazolium-chloride-hydrochloride.

as aneurin or thiamine, which has a complicated structure containing a pyrimidine group and sulphur.



The international unit is 10 mg. of a standard absorption product prepared from rice polishings; 20-30 mg. of this will cure polyneuritis in a pigeon of standard weight (300 grams). About 200 units appear to be needed daily by man. Vitamin B₁ is quite stable in strong acids but is liable to be destroyed by heat in neutral and alkaline solutions. It survives all ordinary cooking. Its precursor in plants is unknown. It is non-toxic in large amounts. All excess taken is destroyed or excreted in the urine and gastric juice. In milk and eggs it is really an excretion for the benefit of the young.

Action.—The vitamin is intimately concerned with the enzyme system responsible for the breakdown of pyruvic acid, an intermediate compound between glucose and carbon dioxide, and in deficiency the pyruvic acid content of the urine is increased. So far as at present known beri-beri is the only example of a disease resulting from the paralysis of a single enzyme system, the animal otherwise being quite normal. Peters and his associates have shown that minute amounts of the vitamin will improve the oxygen uptake, indicating that it is a true tissue catalyst.

Vitamin B₂ Complex.—This was first thought to be a single substance like vitamin B₁ but it is known to consist of several factors. The pellagra-preventing and antidermatitis factors are thermostable and not present in the same amount in alcoholic extracts of yeast as vitamin B₁. The factors of the complex are:—

1. Nicotinic acid. The amide of nicotinic acid is part of the molecule of co-enzyme, which plays an important part in the metabolism of carbohydrates. Deficiency results in pellagra, a disease of maize-eating peoples, characterised by itchy dermatitis, sometimes pustular, great intestinal disturbance, diarrhoea, and degeneration of the bowel-wall.

2. Ribo-flavin forms the prosthetic group of Warburg's yellow oxidation enzyme and is probably an oxidation catalyst. Like nicotinic acid it is present in eggs, liver, milk, and yeast, but appears to be present in all animal and plant cells—in the latter especially when germinating. Considerable quantities are present in young

green leaves. The chief results of its absence are inflammation of the lips and mouth, dry dermatitis, and ocular lesions. Young animals, especially rats, chicks, and dogs, cease to grow in a few days if it is absent from their diets.

The daily requirement of riboflavine, as judged by the amount of intake needed to give the urinary output of the magnitude seen in normal individuals, is considered to be 2 to 3 mg. per day. It is more heat-stable than thiamin. It is not stored in the body, is non-toxic in excess, and is excreted in the faeces. As in the case of B₁, excessive fat in the diet appears to increase the need for the vitamin which also appears to act in conjunction with B₁ in other ways.

3. Vitamin B₆ pyridoxin has somewhat the same properties and sources as the pellagra-preventing factor but does not cure pellagra or its analogue "black tongue" in dogs. Its absence leads to dermatitis, loss of hair, and swelling of the ears and paws which are not cured by nicotinic acid (H. Chick). It is said to act as a sedative in man, and in large doses is toxic to the nervous system of rats.

Probably there are still other factors not yet identified, especially necessary for birds.

The Water-Soluble Antiscorbutic Vitamin C.—This vitamin is contained in fresh fruit and vegetables and in green leaves and germinating seeds; in the days of sailing ships the absence of such substances led to scurvy, the curse of the Navy and Mercantile Marine, and of expeditions. The vitamin is easily oxidised, especially in alkaline solution and if cooking is prolonged, as in stews; hence it is less liable to be destroyed in cooking when acid. Curiously enough, West Indian limes are deficient in this vitamin and the substitution of lime-juice for other fruits led to many outbreaks of scurvy. Oranges and lemons are good sources and especially rose-hips, nettles, black currants, and horse-radish. Even potatoes apparently contain sufficient for some people, but not in winter.

The disease was referred to by Captain Cook and by Vasco da Gama who lost 100 out of 160 of his men from the disease in his famous voyage round the Cape of Good Hope. It is to Lind of the British Navy that we owe the credit of the first demonstration, in 1757, that oranges and lemons were the best treatment for the disease, although the fact was not fully appreciated until 1907 when Holst and Fröhlich produced experimental scurvy in guinea-pigs. Mild scurvy is not an uncommon disease especially under conditions of malnutrition. It may occur in infants fed on proprietary foods and in patients on restricted diets.

Deficiency.—Scurvy is characterised by great weakness, tendency to fractures and hæmorrhage, especially from the gums, because of

fragility of the capillaries, with loosening of the teeth; it is accentuated by hard physical work.

Only for man, the guinea-pig, and a few bacteria is vitamin C absolutely essential. It is particularly important in wound healing and in the repair of fractures, and appears to be concerned with the growth of fibrous tissue and of bone. The essential deficiency is a reduction of oxygen-uptake of tissues generally. It has been found that persons suffering from surgical tuberculosis and chronic rheumatism are deficient in vitamin C and this may be responsible for their failure to recover easily from such infections. The giving of fruit to sick patients generally may indeed have a therapeutic value and a scientific basis.

Chemistry.—The vitamin is now known to be ascorbic acid ($C_6H_8O_6$). The strongly reducing powers of antiscorbutic extracts of lemon juice (Zilva) led to its being identified with other strongly reducing substances in many plants and in the cortex of the adrenals (Tillmans and Hirsch). It even reduces Fehling's solution in the cold.

This powerful reducing action of ascorbic acid was first noted by Szent-Györgyi who found that it reduced 2-6-dichlorophenol indophenol in acid solution (pH_2), and much has since been made of this observation. By its use it has been found that ascorbic acid is excreted in the urine to the extent of 20 to 30 mg. daily. The time taken to decolorise the substance when injected under the skin is also used as a test. It is considered that at least this amount excreted should be supplied daily (Harris).

It is possible to make use of a similar test in finding out the vitamin C content of foods before and after cooking. An extract is made of the food with dilute trichloroacetic acid and filtered. The vitamin content is determined by finding how much is needed to decolorise a known volume of the indicator previously standardised against ascorbic acid. By such studies it can be shown that if vegetables are cooked in alkali or chopped up their vitamin C is destroyed by the oxidase of the tissue juices. The vitamin is more stable in acid solution.

Ascorbic acid has now been synthesised and crystallised, but the form of its crystals depends on the conditions of its crystallisation. They may be needle-shaped or rhomboid.

The international unit is the activity of 0.05 mg. l-ascorbic acid.

Vitamin P is a substance in lemon juice which is much more effective than ascorbic acid in treating certain cases of increased capillary permeability. It is called citrin.

Vitamin E.—The third fat-soluble vitamin is made by plants, and the best-known source of it is an oil extracted from sprouting wheat germs, but it is present in many vegetable oils, e.g. olive oil.

There is a little in animal fats. Its absence results in sterility in rats otherwise fertile. This is due in the female to failure of the foetus to grow normally, although the mother appears to be normal. In the male there is degeneration of the testis. An interesting observation is that of Verzář who has found that the intraperitoneal injection of the vitamin has a similar effect in rats to the injection of an extract of the anterior lobe of the pituitary body, and it is suggested that the vitamin is necessary for normal pituitary function. This vitamin has been found valuable in the treatment of habitual abortion. The pure vitamin has been shown to be three oily colourless alcohols, one, α -tocopherol, having the formula $C_{29}H_{48}O_2$.

Vitamin H—Biotin.—This vitamin is widely distributed in the plant kingdom, but is especially concentrated in seeds. Deficiency in rats causes progressive emaciation, dermatitis, and death. In man there is lassitude and sleepiness, an ashen pallor of the skin, which becomes dry and brawny with a tendency to acne and boils. Symptoms have also been produced experimentally in man, on diets consisting of one-third desiccated egg-white, but it is doubtful if it is ever formed as a result of faulty natural diet. An anti-egg-white-injury factor can be isolated from liver.

Vitamin K (Koagulation-Vitamin.)—It is found that if this vitamin is deficient from the diet of chicks, their blood clots very slowly, due to a deficiency of prothrombin. The natural vitamin which occurs, especially in green leaves (such as cabbage, spinach), egg yolk, liver, and certain bacteria, has been shown to have a naphthoquinone nucleus with a long phytol tail. For the absorption of the vitamin, bile is necessary, therefore in certain diseases of the liver and in biliary obstruction prothrombin may be deficient. The vitamin has now been used in the treatment of hæmorrhagic states in infants.

The Biological Estimation of Vitamins.—In order to determine the amount of vitamin in a given foodstuff, when a chemical test is not available, it is necessary to find out the minimum amount of the foodstuff which will just prevent a particular deficiency disease in an animal placed on a diet sufficient in every other way. For example, to study vitamin A, rats are fed on caseinogen to supply protein, starch, salt mixtures, and substances containing all the vitamins except A.

In most cases, however, the application of facts discovered by animal experiments have proved themselves to be of inestimable value to mankind.

GENERAL REFERENCES.—Rosenberg, 1942. (*The Chemistry and Physiology of the Vitamins*), Mellanby, 1934. (*Nutrition and Disease*), Harris, 1938.

Vitamins and Human Diets.—The whole subject of vitamins is of national importance, and it is evident that many classes of the community do not obtain the infinitesimally small amounts

necessary to maintain good health; although they may avoid gross disease, many indefinite indispositions may be related to the absence or deficiency of these substances.

The following statement is taken from a recent Medical Research Council Report:—"So far as Western civilisation is concerned it is no doubt true that the rareness of the occurrence of frank deficiency diseases such as scurvy, xerophthalmia, and beri-beri indicates that an absolute deficiency of vitamins scarcely ever exists in the individual diet.

"On the other hand, it is now becoming generally recognised that much subnormal health and development, and even incidence of disease, are associated with a partial deficiency of one or more of these accessory substances. The influence of such partial deficiencies even when relatively slight may be extremely serious when they occur in early life and, if we may judge from the results of experiments on animals, an adequate supply of these indispensable dietary components later in life may fail to make good the damage caused by a deficiency in youth." The Report gives numerous examples of the occurrence of such deficiency disease, latent or actual, when for one reason or another patients have been placed on special diets. Such deficiency diseases occasionally occur in individuals living for a long time on restricted diets—cases of gastric ulcer, food cranks, and children fed on proprietary foods.

One remarkable development of the experimental study of the lack of vitamins on animals has been the large number of degenerative changes, especially in the central nervous system, which have been discovered. There is good reason to hope that this may eventually throw light on the many very obscure and commonly fatal nervous diseases which are found in man.

We have already referred to the successful treatment of dental caries by means of vitamin D. This emphasises the point that apparently circumstances can occur, possibly intestinal, which cause a diet which is sufficient for one person to be inadequate for another even in the same family.

It must, however, be emphasised that it is not always possible to apply the information gained on the lower animals directly to man, for some individuals appear to live well on very deficient diets.

It seems just possible that peoples who have been habitually without or short of vitamins may be able to do with less than those who have been victims of the "Eat more Fruit" and "Drink more Milk" campaigns. On the other hand, it becomes evident that the alleged benefits of a vegetarian diet, *e.g.* in rheumatism, may depend on an increased vitamin intake.

Substance.	Vitamin A. Int. Units per 100 gm. (or ml.).	Vitamin D. (Int. Units/100 gm.)	Vitamin B. (Int. Units per 100 gm.)	Riboflavin. (Mg. per 100 gm.)	Nicotinic Acid. (Mg. per 100 gm.)	Vitamin C. (Mg. per 100 gm.)
Milk, cow's	105-279*	Butterfat 41	15-23 (raw)	0.1-0.78	<0.1-0.5	0.17-3.137
Butter	800-20,000*	8-99	...	0.008
Cheese	195-4240*	0.12-0.410
Cod-liver oil	Vit. A 39,930-256,000 Vit. A 291,000-16,130,000
Hallbut liver oil
Meat, beef	12-100	0.0408-0.35	3.8-10.2	1.6-2.2
" ox liver	90-130	0.1-3.0	9.3-27.5	24-68
" ox tongue	95	...	12.8	...
" pig muscle	180	0.0876-0.24	3.3	1.90
" fresh ham	275-510	...	4.7-10.4	...
" smoked ham	357
" chicken	49-77	0.0264-0.1365
Eggs, hen, yolk	8800*	Oil 330	...	White 0.4-0.5	White <0.5-<2.5	...
" whole	Vit. A Carotene 700	Whole dried 220	...	0.031-0.076	Yolk 1-<4	2.20 (Semmelbrot)
Bread, white	24-35	...	1.2	...
" brown	45-140	...	1.0 and 2.0	6.6-41
" wholemeal	35-60	0.0075-0.2
Potato	Vit. A Carotene 700	...	30-60	4.8-60
Peas, fresh	139-2000	...	98-280	0.01-0.23
" dried	40-480	...	1.0	...
Beans, broad	Carotene 170-1080
" haricot	52-120
" runner	25-75	0.030-0.566	...	1.8-40
Lettuce	Carotene 1430-3720	...	90	0.03-0.116	...	<0.5-22
Turnip roots	0	0.040	...	11.49-54.4
" leaves	24,000 dry wt.	39-209.8
Carrot	1,900 2000-13,200	0.018-0.02	<0.5	1.0-40.6
Spinach	13,000 4390-48,000	0.057-0.089	1.7	6-228
Tomato	3,000 300-18,000	...	18-40	0.01-0.236	<0.5	10.6-72
Cabbage	900 10-30	...	20 and 25	0.032-0.215	0.3	20-158
Apple, Bramley's seed- lings	40	0.005	<0.5	0.1-20
Orange juice	300 300-400 Vit. A 80-335	0.0069-0.059	...	22-89
Banana	Carotene 110	...	17-60	0.0075-0.048	...	0.5-22.40
Yeast, dried	Brewer's 700-12,000	12.43	34.93	...
" fresh brewer's	400	1.480	9.1-10.2	...
" baker's	Dry 50	1.6
" "	Moist 7.4-12.0	50-61
						105-188

Kindly compiled by Miss A. S. Cole.

Total A potency.

CHAPTER XXV

FOOD

THE chief chemical compounds or *proximate principles* in food are:—

1. Proteins	} organic.
2. Carbohydrates	
3. Fats	
4. Water	} inorganic.
5. Salts	
6. Vitamins	

In milk and in eggs, which form the exclusive foods of young animals, all varieties of these proximate principles are present in suitable proportions. Hence they are spoken of as perfect foods. Eggs, though a perfect food for the developing bird, contain too little carbohydrate for a mammal. In most vegetable foods carbohydrates are in excess; while in animal foods, such as meat, the proteins are predominant.

The composition of various articles of diet and the principles of dietetics are well given by Hutchison and Mottram, 1933.

Milk.

Milk, which we have already spoken of as a perfect food, is only so for young children. For those who are older, it is so voluminous that unpleasantly large quantities of it would have to be taken in the course of the day to ensure the proper supply of nitrogen and carbon. Moreover, it is relatively too rich in protein and fat. It also contains too little iron (Bunge): so that children weaned late become anæmic.

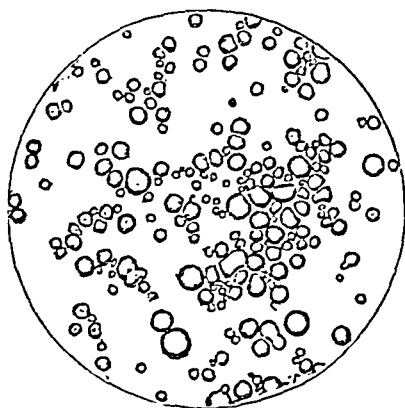


FIG. 149.—Globules of cow's milk. $\times 400$.

The microscope reveals that milk consists of two parts: a clear fluid and a number of minute particles that float in it. These consist of minute oil globules, varying in diameter from 0.0015 to 0.005 millimetre (fig. 149).

The milk secreted during the first few days of lactation is called *colostrum*. This is considered to be of value in relation to infection. It contains very little caseinogen, but

large quantities of albumin and globulin instead. Microscopically, cells from the acini of the mammary gland are seen, which contain fat globules in their interior; they are called *colostrum corpuscles*.

Reaction and Specific Gravity.—The reaction of fresh cow's milk and of human milk is amphoteric. This is due to the presence of both acid and alkaline salts. All milk readily turns acid or sour as the result of fermentative change, part of its lactose being transformed into lactic acid. The specific gravity of milk is usually ascertained with the hydrometer. That of normal cow's milk varies from 1028 to 1034. When the milk is skimmed the specific gravity rises, owing to the removal of the light constituent, the fat, to 1033 to 1037. In all cases the specific gravity of water is taken as 1000.

Composition.—The following table (Bunge) contrasts the milk of woman and the cow; but it must be understood that these are

	Woman.	Cow.
	Per cent.	Per cent.
Proteins (caseinogen and albumin)	1·7	3·5
Butter (fat)	3·4	3·7
Lactose	6·2	4·9
Salts	0·2	0·7
Vitamins A, D, B, C,	+ + + + +	+

average figures and are not strictly applicable to any particular individual. Thus, for example, the Frisian cow produces a more plentiful but more dilute milk than an Ayrshire cow—and human milk varies from time to time in the same individual. Hence, in feeding infants on cow's milk, it is necessary to dilute it, and add sugar and a little cream to make it approximately equal to natural human milk. Separated milk contains only about 0·5 per cent. of fat.

The Proteins of Milk.—The principal protein in milk is called *caseinogen*; it is *precipitable* by acids such as acetic acid, and also by saturation with magnesium sulphate, or half saturation with ammonium sulphate, so resembling globulins; it is *coagulated* by rennet to form *casein*. Cheese consists of casein with the entangled fat. The other protein in milk is *lact-albumin*. It is present in small quantities only; it differs in some of its properties (specific rotation, coagulation temperature, etc.) from serum-albumin. Human milk contains more than cow's.

The Coagulation of Milk.—Milk is coagulated by rennin, an enzyme secreted by the stomach, especially in sucking animals. Advantage is taken of this in the making of cheese, and of curds and whey or junket. The rennet, as it is called commercially, is generally obtained from the calf.

Some plants also contain a rennin, especially seaweeds.

The *curd* consists of the casein and entangled fat: the liquid residue called *whey* contains the sugar, salts, and albumin of the milk. It is doubtful if curdling is a chemical process. It may be mainly a physical (colloidal) change.

The addition of rennet produces coagulation in milk, provided that a sufficient amount of calcium salts is present. If the calcium salts are precipitated by the addition of potassium oxalate, rennet causes no formation of casein. The process of curdling in milk is a double one; the first action due to rennet is the production of a change in caseinogen; the second action is that of the calcium salt, which precipitates the altered caseinogen as casein. In blood, also, calcium salts, as we have seen, are necessary for coagulation.

Caseinogen is a phospho-protein (see p. 278). In milk it is combined with calcium to form calcium caseinogenate; when acetic acid is added, we therefore get calcium acetate and free caseinogen.

The Fats of Milk.—The chemical composition of the fat of milk (butter) is very like that of adipose tissue. There are, however, small quantities of fats derived from fatty acids lower in the series, especially butyric and caproic. Each fat globule appears to be surrounded by a film of protein (Ramsden). Milk also contains small quantities of lipides (lecithin, cholesterol, and a yellow fatty pigment or lipochrome).

Lactose, or Milk Sugar.—This is a disaccharide ($C_{12}H_{22}O_{11}$). Its properties have already been described. (See Carbohydrates.)

Souring of Milk.—When milk is allowed to stand, the chief change which it is apt to undergo is a conversion of a part of its lactose into lactic acid. This is due to the action of bacteria normally present in the air, and would not occur if the milk was boiled and kept contained in closed sterilised vessels. This observation is of great historical interest as Lord Lister used it as his example of bacterial action in his first lecture in London at King's College. When souring occurs, the acid formed precipitates a portion of the caseinogen. This must not be confounded with the formation of casein from caseinogen, which is produced by rennet, but cheese may be made by both processes. There are, however, some bacteria which, like rennet, produce true coagulation.

The Salts of Milk.—The principal salt present is calcium phosphate; a small quantity of magnesium phosphate is also present. The other salts are chiefly chlorides of sodium and potassium.

It appears that milk is deficient in iron. The young animal obtains its iron from the placenta of the mother, and it has been suggested that females store iron in the liver for this purpose. This iron deficiency renders milk an incomplete food during adolescence although suitable for the very young.

The Vitamins of Milk.—Milk contains vitamin A with traces of B, C, and D, but only if the animal from which it is derived is fed on a suitable diet. The milk of cows which may not be given fresh food in winter is therefore liable to be deficient. The vitamin A will withstand boiling for a short period, and even drying if this is done rapidly. Human milk contains 5 to 10 times more vitamin A than cow's milk.

The Adaptation of Cow's Milk for Humans.—Although a wide variety of animals produce milk its variation in composition is very great indeed.

The milk best adapted for the nutrition of the young animal is that which comes from its mother, or, at least, from an animal of the same species. This is not, however, always possible in the feeding of children, and cow's milk has to be substituted, but it is always a poor substitute, and it is not always realised that in spring cow's milk may be much richer in fat than in winter, especially in some herds. Cow's milk must be diluted, and sugar and cream added, so as to make it quantitatively like mother's milk, but even then the question arises whether the essential difference between the two kinds of milk is not deeper than one of mere quantities; and, in particular, the pendulum of scientific opinion has swung backwards and forwards in relation to the question whether the principal protein, called caseinogen in both, is really identical in the two cases. The caseinogen of human milk curdles in small flocculi in the stomach, so contrasting with the heavy curd which cow's milk forms; and even although the curdling of cow's milk be made to occur in smaller fragments by mixing the milk with barley water or lime water, its digestion proceeds with comparative slowness in the child's alimentary canal. These are practical points well known to every clinical observer, and in the past they have been attributed, not so much to fundamental differences in the caseinogen itself, as to accidental concomitant factors; the excess of citric acid in human milk, for instance, and its paucity in calcium salts, have been held responsible for the differences observed in the physical condition of the curd and in its digestibility. The lact-albumin of cow's milk is often responsible for eczema in children.

Lactation, or the production of milk from the mammary glands, is discussed later in relation to Reproduction.

The Mammary Glands.

The mammary glands are composed of large divisions or lobes, and these are again divisible into lobules; the lobules are composed of the convoluted and dilated subdivisions of the main ducts held together by connective tissue. Covering the general surface of the gland, with the exception of the nipple, is a considerable quantity of fat, itself lobulated by sheaths and processes of areolar tissue.

The main ducts of the gland, fifteen to twenty in number, called the *lactiferous* ducts, are formed by the union of the smaller (lobular) ducts, and open by small separate orifices through the nipple. At the points of junction of lobular ducts to form lactiferous ducts, and just before these enter the base of the nipple, the ducts are dilated; and during the period of active secretion by the gland, the dilatations form reservoirs for the milk, which collects in and distends them. The walls of the gland-ducts are formed of areolar with some unstriped muscular tissue, and are lined internally by short columnar and near the nipple by flattened epithelium.

During pregnancy the mammary glands undergo changes (*evolution*) which are readily observable. They enlarge, become harder, and more distinctly lobulated; the veins on the surface become more prominent. The areola becomes enlarged and dusky, with projecting papillæ; the nipple, too, becomes more prominent, and milk can be squeezed from the orifices of the ducts. This is a very gradual process, which commences just after conception, and progresses steadily during the whole period of gestation. In the gland itself solid columns of cells bud off from the old alveoli to form new alveoli. But these solid columns after a while are converted into tubes by the central cells becoming fatty and being discharged as the colostrum corpuscles above mentioned. After the end of lactation, the mamma gradually returns to its original size (*involution*). The acini, in the early stages of involution, are lined with cells in all degrees of vacuolation. As involution proceeds, the acini diminish considerably in size, and at length, instead of a mosaic of lining epithelial cells (twenty to thirty in each acinus), we have five or six nuclei (some with no surrounding protoplasm) lying in an irregular heap within the acinus. No secretory nerves of the mammary gland have yet been discovered. The various changes which take place are produced by hormonal influences.

Eggs.

The chief constituent of the *shell* is calcium carbonate. The *white* is composed of a richly protein fluid enclosed in a network of firmer and more fibrous material.

The amount of solids is 13·3 per cent.; of this, 12·2 is protein in nature (egg-albumin, with smaller quantities of egg-globulin, and of a mucinoid substance called ovo-mucoid), and the remainder is made up of sugar (0·5 per cent.), traces of fats, lecithin, and cholesterol, and 0·6 per cent. of inorganic salts.

The *yolk* is rich in food materials for the development of the future embryo especially a phospho-protein called *vitellin*.

The nutritive value of eggs is high, as they are so readily digestible; but the more an egg is cooked the more insoluble do its protein constituents become. They are an important source of vitamins.

Meat.

Meat is composed of the muscular and connective (including adipose) tissues of certain animals. The flesh of some animals is not eaten. This is largely a matter of fashion and of flavour.

Meat is the most concentrated and most easily assimilable of nitrogenous foods. It is our chief source of nitrogen. Its chief solid constituent is protein, and the principal protein is myosin. In addition

to the extractives and salts contained in muscle, there is always a certain percentage of fat, even though all visible adipose tissue is dissected off. The fat-cells are placed between the muscle-fibres, and the amount of fat so situated varies in different animals; it is particularly abundant in pork; hence the indigestibility of this form of flesh: the fat prevents the gastric juice from obtaining ready access to the muscle-fibres. The hanging of meat leads to the formation of lactic acid and acid phosphates from organic phosphates and these facilitate the formation of gelatin from collagen during cooking.

Different meats vary very little in composition. All contain 70 to 80 per cent. of water, about 20 per cent. protein and .5 to 1 per cent. carbohydrate. The flesh of young animals contains more gelatin than that of old. The flavour of meat is due to extractives which have an unknown chemical composition. Cooking in any way causes a loss of about $\frac{1}{4}$ of the water.

The large percentage of water in meat should be particularly noted; if a man wished to take his daily supply of 100 grams of protein entirely in the form of meat, it would be necessary for him to consume about 500 grams (*i.e.* a little more than 1 lb.) of meat.

Flour.

White wheat flour is made from the interior of wheat grains, and contains the greater proportion of the starch of the grain and most of the protein. Whole flour is made from the whole grain *minus* the husk, and thus contains not only the white interior but also the harder and browner outer portion of the grain and the germ or embryo plant. This region contains a somewhat larger proportion of protein. Whole flour contains 1 to 2 per cent. more protein than the best white flour, but it has the disadvantage of being less readily digested. Brown flour contains a certain amount of bran in addition; it is still less digestible, but is useful as a mild laxative, the insoluble cellulose mechanically stimulating the intestinal canal as it passes along.

The best flour contains very little sugar. The presence of sugar indicates that germination has commenced in the grains. In the manufacture of malt from barley this is purposely allowed to go on.

When mixed with water, wheat flour forms a sticky, adhesive mass called dough. This is due to the formation of gluten. Gluten is a mixture of two proteins—namely, gliadin, which is soluble in alcohol, and glutenin, which is soluble in alkali. The adhesive character of gluten is due to gliadin; grains which are poor in gliadin (*e.g.* rice) cannot be used for bread-making.

The following table contrasts the composition of some of the more important vegetable foods:—

Constituents.	Wheat.	Barley.	Oats.	Rice.	Lentils.	Peas.	Potatoes.
Water. .	13·6	13·8	12·4	13·1	12·5	14·8	76·0
Protein .	12·4	11·1	10·4	7·9	24·8	23·7	2·0
Fat . .	1·4	2·2	5·2	0·9	1·9	1·6	0·2
Starch .	67·9	64·9	57·8	76·5	54·8	49·3	20·6
Cellulose .	2·5	5·3	11·2	0·6	3·6	7·5	0·7
Mineral salts	1·8	2·7	3·0	1·0	2·4	3·1	1·0

We see from this table—

1. The great quantity of starch always present.
2. The small quantity of fat; that bread is generally eaten with butter is a popular recognition of this fact.
3. Protein, except in potatoes, is pretty abundant, and especially so in the pulses (lentils, peas, etc.). The protein in the pulses is not gluten, but consists mainly of globulins.

In mineral matter in vegetables, salts of potassium and magnesium are, as a rule, more abundant than those of sodium and calcium.

Bread.

Bread is made by cooking the dough of wheat flour mixed with yeast, salt, and flavouring materials. An enzyme in the flour acts at the commencement of the process, when the temperature is kept a little over that of the body, and forms dextrin and sugar from the starch, and then the alcoholic fermentation, due to the action of the yeast, begins. The bubbles of carbonic acid, burrowing passages through the bread, make it light and spongy. This enables the digestive juices subsequently to soak into it readily and affect all parts of it. In the later stages, viz., baking, the temperature is raised, the gas and alcohol are expelled from the bread, the yeast is killed, and a crust forms from the drying of the outer portions of the dough.

White bread contains, in 100 parts, 8 to 10 of protein, 55 of carbohydrates, 1 of fat, 2 of salts, and the rest water.

Cooking of Food.

The cooking of foods is a development of civilisation, and serves many useful ends:—

1. It destroys parasites and prevents danger of infection. This relates not only to bacterial growths, but also to larger parasites, such as tapeworms and trichinæ.

2. In vegetable foods it breaks up the starch grains, bursting the cellulose and so allowing the digestive juices to come into contact with the granulose.

3. In animal foods it converts the insoluble collagen of the universally distributed connective tissues into the soluble gelatin. The loosening of the fibres is assisted by the formation of steam between them. By thus loosening the binding material, the more important elements of the food, such as muscle-fibres, are rendered accessible to the gastric and other juices. Meat before it is cooked is generally kept a certain length of time to allow *rigor mortis* to pass off.

Of the two chief methods of cooking, roasting and boiling, the former is the more economical, as by its means the meat is first surrounded with a coat of coagulated protein on its exterior, which keeps in the juices to a great extent, letting little else escape but the dripping (fat).* Whereas in boiling, unless both bouillon and bouilli are used, there is considerable waste. Cooking, especially boiling, renders the proteins more insoluble than they are in the raw state; but this is counterbalanced by the advantages which cooking possesses.

In making *beef tea* and similar extracts of meat it is necessary that the meat should be placed in cold water, and this is gradually and carefully warmed. In boiling a joint it is usual to put the meat into boiling water at once, so that the outer part is coagulated, and the loss of material minimised.

An extremely important point in this connection is that beef tea and similar meat extracts should not be regarded as foods. They are valuable as pleasant stimulating drinks for invalids, but they contain very little of the nutritive material of the meat, their chief constituents, next to water, being the salts and extractives of flesh.

Soup contains the extractives of meat, a very small proportion of the myosin, and the principal part of the gelatin. The gelatin is usually increased by adding bones and fibrous tissue to the stock. It is the presence of this substance which causes soup when cold to gelatinise.

Adjuncts to Food.

Among these must be placed: *alcohol*, the value of which within moderate limits is not as a food but as a stimulant; *condiments* (mustard, pepper, ginger, curry powder, etc.), which are stomachic stimulants, the abuse of which is followed by dyspeptic troubles; and *tea, coffee, cocoa*, and similar drinks; these are stimulants chiefly to the nervous system. Tea, coffee, maté (Paraguay), guarana (Brazil), cola nut (Central Africa), bush tea (South Africa), and a few other plants used in various countries all owe their chief

* This statement has recently been called into doubt.

property to an alkaloid called *theine* or *caffeine* (trimethyl-xanthine); cocoa to the closely related alkaloid, *theobromine* (3-7-dimethyl-xanthine); coca to *cocaine*. These alkaloids are all poisonous, and used in excess, even in the form of infusions of tea and coffee, produce over-excitement, loss of digestive power, and other disorders well known to physicians. Coffee differs from tea in being rich in aromatic matters; tea contains a bitter principle, tannin; to avoid the injurious solution of too much tannin tea should be allowed to infuse (draw) for a few minutes only. Cocoa is not only a stimulant, but a food in addition; it contains about 50 per cent. of fat, and 12 per cent. of protein. In manufactured cocoa, the amount of fat is reduced to 30 per cent., and the amount of protein rises proportionately to about 20 per cent. The quantity of cocoa usually consumed is too small for these food materials to count very much in the daily supply. The amount of protein in solution (mainly proteose) in a breakfast cup of cocoa is under half a gramme; most of the foodstuffs are in suspension, for cocoa is drunk "thick," not as a clear infusion.

Green vegetables are taken as a palatable and valuable adjunct to other foods, rather than for their nutritive properties (see Vitamins). Their potassium salts are, however, abundant. Cabbage, spinach, and asparagus contain 80 to 92 water, 1 to 2 protein, 2 to 4 carbohydrates, and 1 to 1.5 cellulose per cent. The small amount of nutriment in most green foods accounts for the large meals made by, and the vast capacity of the alimentary canal of, herbivorous animals.

Fruits, like vegetables, contain chiefly water. They contain also organic acids, *e.g.* citric, and their salts, which become oxidised to carbonates in the body. Fruits therefore, with the exception of prunes and cranberries, promote an alkalinity of the body like a vegetable diet generally. Fruits and vegetables are also important sources of vitamins, and in virtue of their cellulose add appreciably to the bulk of the intestinal contents and so promote intestinal movements.

REFERENCE.—Emerson, 1935 (alcohol).

CHAPTER XXVI

THE STRUCTURE OF THE ALIMENTARY CANAL IN RELATION TO ITS FUNCTION

IN the lowest animals foodstuffs are absorbed through the surface from the environment, but the higher animals have developed a specialised canal in which the food is prepared for absorption into the blood. This is necessary because in nature the food is either protected or insoluble, otherwise it would be washed into the soil by the rain.

This **alimentary canal**, as it is called, is essentially an inlet of the body surface with which it is continuous at both ends. Physiologically the contents of the alimentary canal may be considered outside the body, *i.e.* the tissues of the animal. The area over which the food is spread is enormous. If the mucous membrane of the small intestine alone was unfolded and laid flat its area would be 1.5 square metres, but in addition it has projecting from its inner surface minute finger-like processes, the villi, which it has been calculated make the total up to about 40 square metres.

The canal is designed to hold a quantity of food, so that eating need not be continuous, to digest it, and so render it suitable for absorption into the blood stream, and to return to the outside world those portions which are not digestible. In addition it is a route by which the body gets rid of any mineral substances which may be absorbed in excess. Different parts of the canal specialise in different activities, thus the stomach is the chief container, the small intestine the chief absorbent region, while the large intestine is primarily concerned with the absorption of water and also with excretion, but there is considerable overlapping. Thus we see a common general structure with an exaggeration of some features in special regions. These are seen in fig. 150, p. 400. There are considerable variations in different animals, among the more striking being the dual stomach and the enormous size of the colon in herbivora.

The food is received into the alimentary canal, which may vary in complexity from a simple tube in the lower animals to that found in mammals. In man the alimentary canal consists of a long muscular tube lined by mucous membrane beginning at the mouth and terminating at the anus. It comprises the mouth,

pharynx, œsophagus or gullet, stomach, small intestine, and large intestine. Opening into it are numerous glands which pour juices into it; these bring about the digestion of the food as it passes along. Some of the glands, such as the gastric and intestinal glands, are situated in the mucous membrane which lines the canal; others, such as the salivary glands, liver, and pancreas, are situated at a distance from the main canal, and pour their secretion into it by means of side tubes or ducts.

The outermost coat of the greater portion of the abdominal part of the canal has a *serous coat*, or peritoneum of shiny pavement epithelium, which is moistened on its surface by lymph, and thus the canal can move freely with the minimum of friction on those structures with which it comes in contact in the abdomen and other parts of itself and the abdominal wall, which is likewise lined by a layer of peritoneum.

The motive power of the canal, by which the food is passed on from one part to another, is supplied by its muscular coats.

The Muscular Coat.—This consists of two layers: in the outer, the fibres are arranged longitudinally, and in the inner, circularly. In the stomach, especially at the cardiac end, there is a third coat, in which the fibres have an oblique direction. At the pyloric orifice

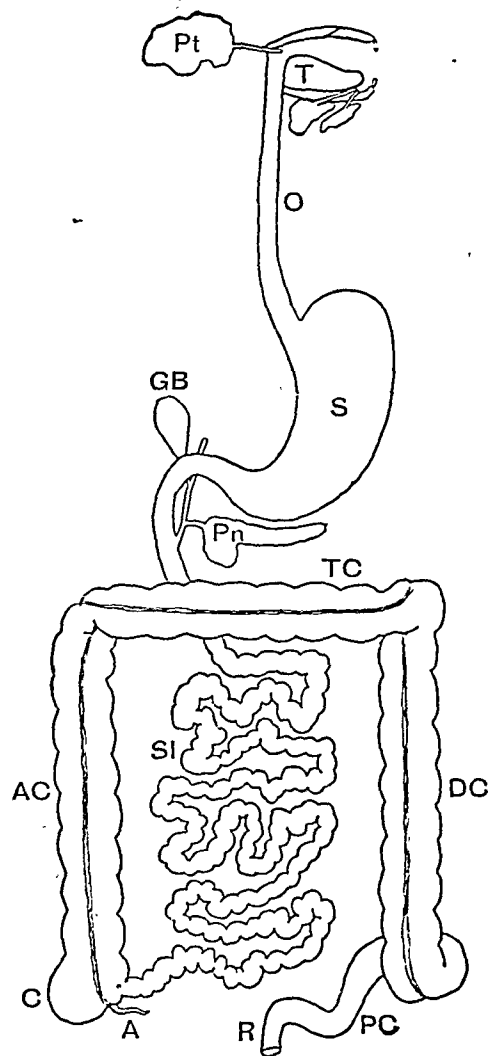


FIG. 150.—Alimentary Canal. Pt, parotid gland; T, tongue; O, œsophagus; S, stomach; GB, gall-bladder; Pn, pancreas; SI, small intestine; AC, ascending colon; TC, transverse colon; DC, descending colon; PC, pelvic colon; R, rectum; C, cæcum; A, appendix.

of the stomach (that is, where the small intestine begins) the circular fibres are increased in amount to form a sphincter; but at the cardiac orifice where the œsophagus enters there is no special ring, but a considerable area in the region is normally kept in a state of contraction, and by its relaxation not only allows food to

enter but makes room for it. The muscle-fibres are of the plain variety, except in the pharynx and upper part of the œsophagus where they are striated.

The Mucous Membrane.—This consists of an *epithelium* on its surface which is stratified in the mouth, pharynx, œsophagus, which is in contact with the rough food, and lower part of the anal canal, but columnar in other parts. It would seem that this mucous membrane, like epithelium elsewhere, becomes adapted to the kind of food its possessor habitually takes. Beneath the epithelium is a *corium* of connective tissue, in which there is lymphoid tissue; in the intestine the lymphoid nodules are often spoken of as solitary follicles, except in the lower part of the small intestine (the ileum), where they are congregated together as Peyer's patches and have the function of protecting the canal against bacterial invasion from the bacteria which abound in the large intestine, where, in the herbivorous animals, they perform the very important function of digesting cellulose. At the back of the mouth, the tonsils are masses of lymphoid nodules covered with mucous membrane. In the deepest part of the mucous membrane is a thin layer of involuntary muscle called the *muscularis mucosæ*, through which the ducts of some of the deeper glands of Brunner pass in the region of the duodenum.

The two main coats (muscular and mucous) are connected together by a loose layer of connective tissue known as the *submucous coat*. In this the larger blood-vessels are situated which give off branches to the other two coats but more abundantly to the mucous membrane. The submucous coat also contains a nerve plexus called the plexus of Meissner.

The secreting glands in the wall of the alimentary canal have the function of producing secretion of juices which are of two kinds, those which contain enzymes which assist in the digestion of the food, and those which contain mucus which is merely protective and lubricative.

Glands are essentially insets of columnar epithelium the cells of which have become modified and manufacture secretion from the blood. They may, however, vary much in complexity as fig. 151, p. 403, indicates.

Mucous glands are present throughout the canal and are especially important at each end. They are usually simple little glands lying just under the mucous membrane throughout the intestine, but in the large intestine there are large goblet cells, so-called because the open end after the discharge of mucus gives the cell a cup or goblet-like appearance.

The gastric glands are tubular glands which differ in structure in different regions of the stomach, and which we shall consider at greater length in our description of gastric digestion.

The glands of the small intestine.—Throughout the whole of the small intestine there are a large number of simple tubular glands (lined with columnar cells) which open between the villi. They are called the crypts of Lieberkühn. In the first part of the small intestine, known as the duodenum, an additional set of glands, called the glands of Brunner, is found. They are embedded in the submucous coat, and the duct of each gland passes inwards to open on the surface of the mucous membrane. Each gland is a branched and convoluted tube lined with columnar epithelium.

The glands of the large intestine consist for the most part of mucous cells, but there are also excreting cells which discharge unwanted material from the body.

The associated glands are those which lie at a small distance from the alimentary canal but pour their secretions into its lumen by way of ducts. They are the salivary glands whose ducts open into the mouth and the liver and pancreas which pour their secretion into the duodenum.

The villi are, as we have said, the minute projecting processes which confer an enormous area on the mucous membrane of the small intestine. Their limitation to the area where most of the absorption of foodstuffs takes place suggests their association with this process, and this is supported further by their detailed structure. Like the rest of the intestine their surfaces are covered by a layer of columnar epithelium. In the centre of a villus is a vessel or lacteal, so-called by its containing the milk-like chyle when fat is being absorbed, while between the lacteal and the mucous membrane is a network containing leucocytes, blood-vessels, nerves, and strands of smooth muscle, all of which are intimately concerned with the phenomenon of absorption which is discussed in detail in a later section. The columnar cells covering the villi play an important part in selecting the substances to be absorbed, but interspersed between them are cells which secrete mucus.

These various facts are illustrated in the following figure.

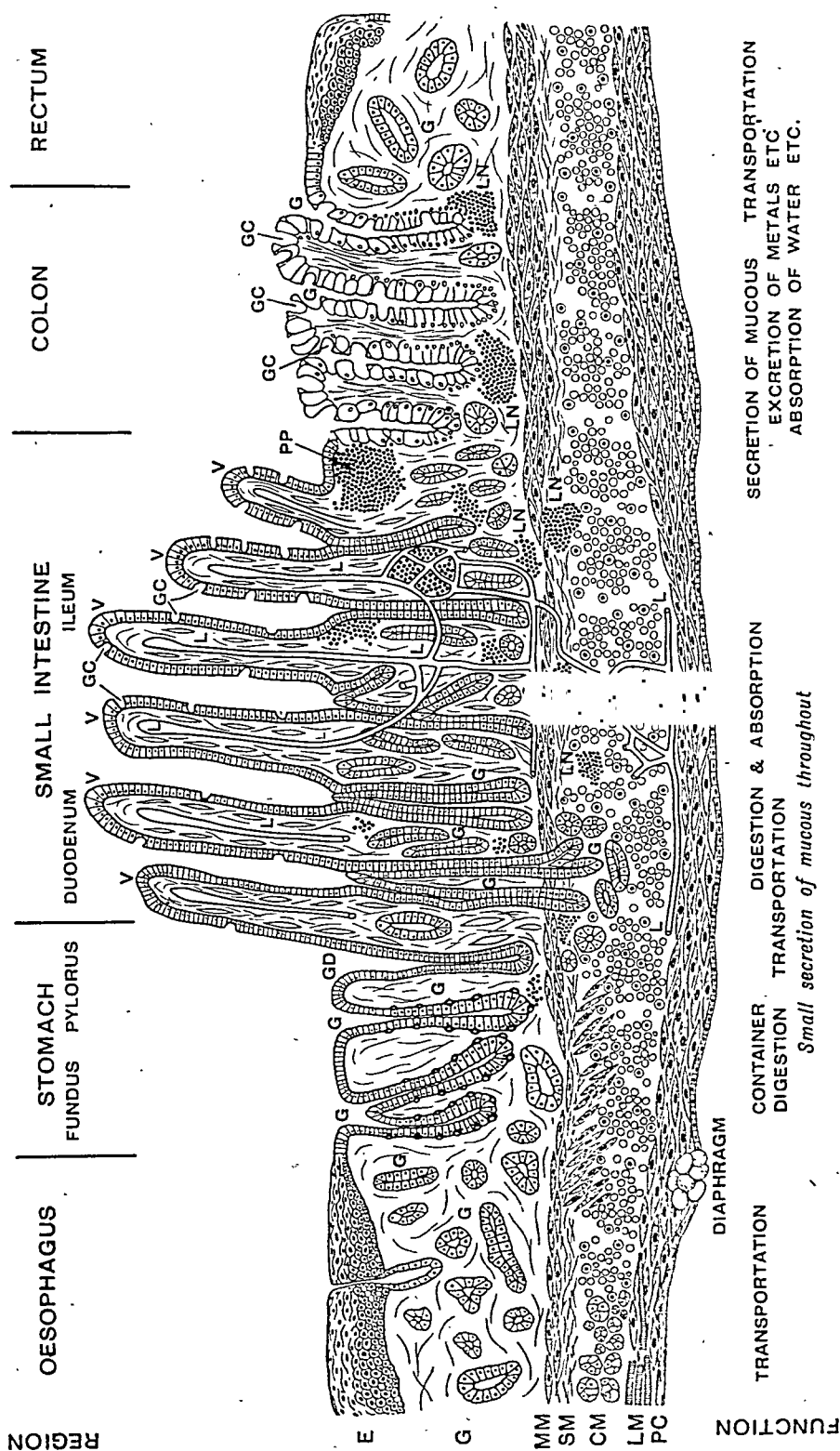


Fig. 151.—Diagram of the histological structure of the various parts of the alimentary canal in relation to its function. E, epithelium; G, glands; MM, muscularis mucosa; SM, submucous region; CN, circular muscle; LM, longitudinal muscle; PC, peritoneal coat; GD, gland duct; V, villi; LN, lymph nodule. PP, Peyer's patch. GC, Goblet (mucous) cell. L, Lymphatics (lacteal).

CHAPTER XXVII

SECRETION

As we have pointed out there is poured into the lumen of the alimentary canal a variety of juices called secretions. We shall now consider the nature of the secretory process in general; the details have been worked out in the salivary glands since these are conveniently situated for investigation.

A secreting apparatus consists essentially of a layer of secreting cells surrounding a central cavity into which the secretion is poured. The cells, which contain granules representing the precursors of the substances secreted, lie on a basement-membrane in close relation to the blood-vessels which nourish the gland and which provide it with the raw materials of its secretion. That the granules in the cells are not the actual substance secreted but a precursor has been shown by chemical means in the case of the glands of the stomach, and by the reaction to histological reagents in the case of mucus-secreting glands. If the substance secreted is an enzyme the precursor is termed a *zymogen*. Intervening between the blood and the gland-cells is the lymph.

Fig. 152 semi-diagrammatically shows some of the more important anatomical distinctions in the form of secreting glands, tubular, racemose, and so forth.

The process of secretion consists of a number of events which may be divided into two categories:

1. The transference of water and certain substances dissolved in the water from the blood of the surrounding capillaries to the lumen of the acinus.
2. The modification of the chemical composition of this solution by the addition to it of substances manufactured by the gland-cells, and by the prevention of substances in the lymph from traversing the gland-cell and reaching the lumen.

The Nature of the Process of Secretion.

Great interest has always been aroused by the problem of secretion, as it is one of those processes in the body which at first sight might be explained on a physico-chemical basis, but which on further

analysis is shown to be very much more complicated. From a study, largely of the secretion of saliva, certain facts have been established in relation to secretion in general. (1) The osmotic pressure of the saliva is less than that of the blood, so that physically, water would

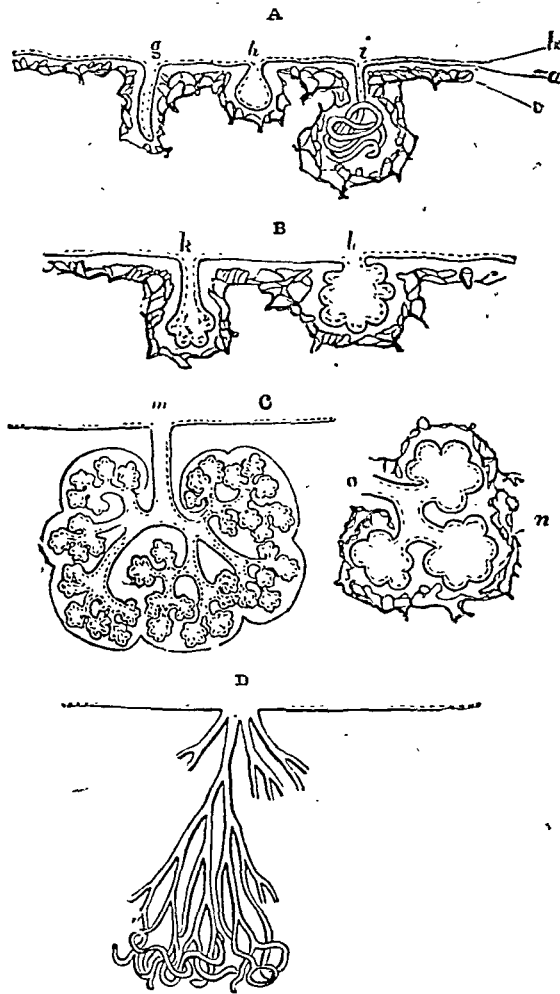


FIG. 152.—Diagram of types of secreting glands. A, Simple glands, viz., *g*, straight tube; *h*, sac; *i*, coiled tube. B, Multilocular crypts; *k*, of tubular form; *l*, saccular. C, Racemose, or saccular compound gland; *n*, entire gland, showing branched duct and lobular structure; *o*, a lobule, detached with *o*, branch of duct proceeding from it. D, Compound tubular gland. (Sharpey.)

tend to pass from the saliva into the blood for reasons which have already been discussed; (2) the pressure of the secretion in the duct of the gland may exceed the blood-pressure; and (3) substances occur in the secretion in greater concentration, *e.g.* enzymes, than they do in the blood, or substances may be elaborated which do not exist in the blood as such at all, *e.g.* the hydrochloric acid of the stomach. These last two facts dispose of any contention

that the secretion is merely filtered off from the blood by a physical process. Further it has been calculated that it would require a pressure some twenty times greater than that of the arterial blood to produce from the blood a salt solution of the same concentration as that of saliva. (4) On the other hand, it can be shown that any increased concentration of the blood, *i.e.* raising the osmotic pressure of the blood, reduces secretion. (5) Finally, it has been shown that the more active the gland is the more oxygen is consumed, and it

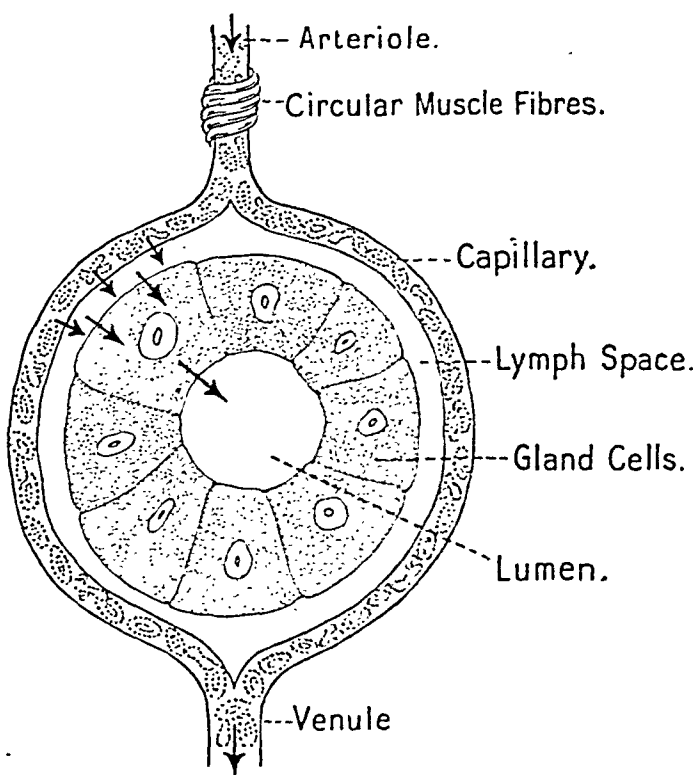


FIG. 153.—Diagram of a secreting acinus.

is evident that the gland uses fuel and does work in a physical sense. Electrical changes are also produced.

It can be shown that this work is done not by the endothelial cells of the vessels but by the cells of the gland, for the gland if placed in a plethysmograph becomes reduced in size when it secretes. A mere dilatation of the vessels set up by stimulation of the nerve brings about in a gland such as the submaxillary, after the administration of atropine to stop secretion, an increased volume. If, then, in secretion there is first an increase in permeability of the vessels consequent on their dilatation a preliminary increase in volume would be expected. This, as we have seen, does not occur.

If the salivary glands are examined histologically, granules can be seen to accumulate in the cells of the gland during rest, and during secretion the granules swell, are extruded from the free edge of the cell, and then dissolved. It is generally agreed that the cell does active work in manufacturing the granules, but how the water is "pumped" into the lumen is very difficult to determine. The idea of the "pump" may be conveniently applied to this process which we do not yet understand but which forces fluid into the lumen of the gland against forces which tend to retain it in the blood.

It has been suggested that the granules break down into smaller molecules which raise the osmotic pressure and cause water to be attracted from the blood. In part of the cell a solution more dilute than the blood is formed and extended, causing an increased concentration in the remaining parts of the cells which attract further water from the blood and lymph.

Another view is that the side of the cell next to the basement membrane is impermeable to the osmotically active substances manufactured by the cell, while the side next the lumen is not. From a tube closed at each end by such membranes a flow has been found to continue till the osmotically active substance is expelled and it is possible that secretion may be similarly produced.

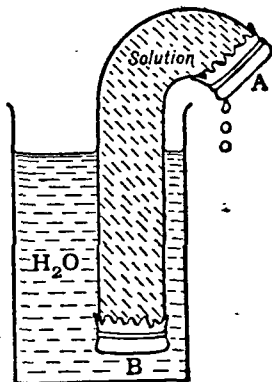


FIG. 154.—(From Wishart.)

We do not, however, really know; and still less have we any idea how secretion can be controlled by nerves, unless it be that the nerves cause the production of substances which influence the permeability of cells of the gland.

All glands are under the control of two sets of nerves, the sympathetic and the parasympathetic. In the alimentary canal the sympathetic stops true secretion although it may cause existing secretion to be driven from the gland. Stimulation of the parasympathetic, or the use of a drug such as pilocarpine which has a similar action, increases secretion, while atropine causes a cessation of glandular activity. In surgical operations, especially on the nose and throat, atropine is an important means of reducing the secretion in these regions.

REFERENCES.—Vincent, 1924, and Wishart, 1931.

CHAPTER XXVIII

SALIVA

THE saliva is formed by three pairs of salivary glands, called the parotid, submaxillary, and sublingual glands.

The parotid glands are serous glands and secrete most of the saliva, the sublingual glands are mucous, and the submaxillaries mixed in type.

If a resting fresh mucous gland is teased and examined in serum the cells are seen to be packed with large granules of *mucinogen*, which, when the gland is active, is transformed into mucin. The serous cells, which in a mixed gland appear as demilunes or crescents round the mucous cells, are smaller, and are full of fine granules of *zymogen* which becomes converted into ptyalin the important digestive enzyme of the saliva.

After secretion the cells shrink, they stain more readily, their nuclei become more conspicuous, and the outer part of each cell becomes clear and free from granules (fig. 155).

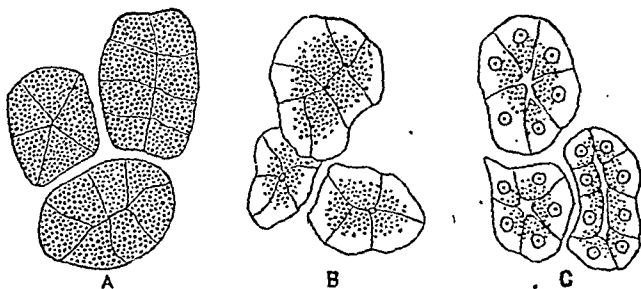


FIG. 155.—Alveoli of parotid gland. A, before secretion; B, in the first stage of secretion; C, after prolonged secretion. (Langley.)

The Secretion of Saliva.

The submaxillary gland has a double nerve-supply: (1) A parasympathetic supply from the chorda tympani, a branch of the seventh cranial, travels with the lingual nerve and passes to Langley's ganglion in the hilus of the gland, where post-ganglionic fibres arise to be distributed to cells and blood-vessels.

(2) A sympathetic supply is derived from the plexus around

the facial artery and accompanies the arterial branches which supply the gland (see fig. 156).

When the chorda tympani is stimulated, secretion of saliva and dilatation of the arterioles take place invariably, but the action of atropine indicates that these two effects are quite distinct, although, no doubt, metabolites normally assist in causing the vasodilatation. Differences occur according to the strength and frequency of the stimulating current, but on the whole it would seem that the chorda controls the amount of secretion produced. Recent investigations have shown that the part played by the sympathetic differs so widely in different animals that the many theories formerly advanced of the relative part played by the two nerves must be regarded as mere matters of speculation (Babkin.) In the dog the secretion caused by sympathetic stimulation is thick, but in the cat it is thin.

Section of the chorda tympani produces no immediate result; but after a few days a scanty but continuous secretion of thin watery saliva takes place; this is called *paralytic secretion*. If the operation is performed on one side, the gland of the opposite side also shows a similar condition, and the thin saliva secreted there is called the *antilytic secretion*. This suggests that the chorda exercises a trophic or nutritive function in relation to the cells of the gland.

Besides the secretory mechanism regulated chiefly by the parasympathetic there is another which expresses the saliva from the gland. This mechanism is probably under the control of the sympathetic (Babkin), but it is not yet clear what histological elements are responsible for this pressor effect.

Effect of Drugs on the Gland. *Atropine*.—After intravenous injection of this alkaloid, stimulation of the chorda tympani no longer produces secretion of saliva. Much larger doses are necessary to abolish the vasodilator effect of chorda stimulation, or the sympathetic flow in those cases where previous stimulation of this nerve evoked a secretion of saliva.

Pilocarpine produces a copious flow of saliva, accompanied by vasodilatation. The duration of the action of **choline** is too short to

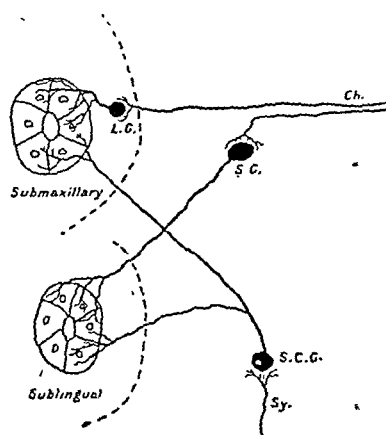


FIG. 156.—Diagram of secretory nerves of submaxillary and sublingual glands. Two fibres of the chorda tympani (Ch.) are shown, one of which supplies the sublingual gland, of which an acinus is shown; the cell-station for this is in S. G., the so-called submaxillary ganglion. The other fibre supplies an acinus of the submaxillary gland; its cell-station is in Langley's ganglion (L. G.), within the substance of the gland. Sy. is a fibre of the sympathetic, which has its cell-station in the superior cervical ganglion, S. C. G. (After Dixon.)

be effective, but we may presume that this substance is produced locally when the chorda tympani is stimulated.

Ergotoxine paralyses the effects of sympathetic stimulation, but not those of stimulation of the chorda tympani.

Adrenaline produces constriction of the blood-vessels. In some animals it evokes a considerable flow of saliva, and when this occurs the constriction of the vessels is followed by dilatation. This favours a view which has been advanced by some observers, that vasodilatation is in part produced by the chemical action of the products of activity (carbonic and lactic acids, etc.). -

The **sublingual gland** is innervated by the same nerves as the submaxillary, but the preganglionic fibres of the chorda tympani have their cell-station in the so-called submaxillary ganglion which is situated between the lingual nerve and the deep part of the submaxillary gland (see fig. 156). This has been determined by Langley's nicotine method (see Autonomic Nervous System).

The **parotid gland** also receives two sets of nerve-fibres analogous to those we have studied in connection with the submaxillary gland. The principal secretory nerve-fibres are glosso-pharyngeal in origin, and reach the gland eventually by the auriculo-temporal nerve; the sympathetic is mainly vasoconstrictor, but in the cat it does contain a few secretory fibres also.

Mechanism of Salivary Secretion.—Under ordinary conditions the secretion of saliva is a reflex action. The principal afferent nerves are those of taste; but the smell or sight of food will also cause "the mouth to water"; and under certain conditions, as before vomiting, irritation of the stomach has a similar effect. These sensory nerves stimulate a centre in the medulla from which efferent secretory impulses are reflected along the secretory nerves (chorda tympani, etc.) to the glands. The subject has been extensively studied by Pavlov and his pupils, especially Babkin.

An external fistula of the submaxillary duct is made in the dog, and it is found that the sight of food, the smell of food, or the administration of any kind of food, causes secretion; acid or even sand introduced into the mouth produces a similar effect. The results on the parotid secretion are as follows: if the dog is shown meat or the meat is given to it to eat there is only a scanty secretion of thick lubricating saliva (0.5 c.c. per minute). If, however, the meat is given as a dry powder, the secretion is much more copious (2 c.c. per minute) thin diluting saliva. In such experiments the dog must be hungry, for the psychical element involved is important. It probably is the case that all constituents of the food causing secretion produce a flow from all the salivary glands, but different substances cause different amounts of saliva to flow, and this would naturally result from varied stimulation of touch and taste sensory nerve-endings.

Pavlov has shown that practically any stimulus may become a "conditioned" stimulus of salivary secretion if the stimulus, *e.g.* the ringing of a bell, has been previously associated with the giving of food. This became the basis of the study of Conditioned Reflexes.

A marked reduction in the amount of saliva secreted takes place under conditions of emotional stress; this used to be the basis of one form of trial by ordeal in which the accused was asked to eat a given amount of dry flour, and accounts also for the marked dryness of the mouth of public speakers in circumstances which bear no relation to their actual water requirements.

Extirpation of the Salivary Glands.—These may be removed in the lower animals without any harmful effects.

Thirst. (See Visceral Sensations.)

The Saliva.

The **saliva** is the first digestive juice to come in contact with the food. The secretions from the different salivary glands are mixed in the mouth; the secretion of the minute mucous glands of the mouth and a certain number of epithelial scales and the so-called "salivary corpuscles" derived from the tonsils are added to it. The liquid is transparent, slightly opalescent, of slimy consistency, and may contain lumps of nearly pure mucin. On standing it becomes cloudy owing to the precipitation of calcium carbonate, the carbonic acid, which held it in solution as bicarbonate, escaping.

The three forms of saliva which contribute to the mixture vary in the amount of solids they contain, sublingual has most and parotid least. The latter contains no mucin. Mixed saliva contains in man an average of about 0.5 per cent. of solids: it has a specific gravity of 1002 to 1006 and its reaction varies from *pH* 5.8 to 7.6 according to the *pH* of the blood (Mathur).

The solid constituents dissolved in saliva may be classified thus:

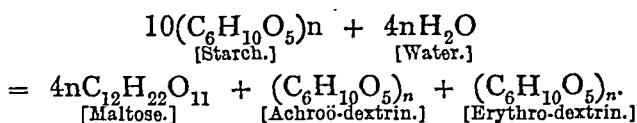
- | | | |
|-----------|---|--|
| Organic | { | a. Mucin : this may be precipitated by acetic acid. |
| | | b. Ptyalin : a starch-digesting enzyme. |
| | | c. Protein : of the nature of a globulin. |
| | | d. Potassium sulphocyanide. |
| Inorganic | { | e. Sodium chloride : the most abundant and important salt. |
| | | f. Other salts : sodium carbonate, calcium phosphate and carbonate; magnesium phosphate; potassium chloride. |
| Bacteria | . | Bacteria and viruses may also be present. |

The Functions of the Saliva.

The functions of the saliva are several. By its chemical action it initiates the digestion of starch, it moistens the food and the mouth thereby facilitating swallowing and speech, while it plays an important part in cleansing the teeth and maintaining the water balance of the body.

The chemical action of saliva is due to its active principle, **ptyalin**, which belongs to the class of enzymes which are called **amylases** (starch-splitting) or **diastases** (resembling diastase, the similar enzyme in germinating barley and other grains).

The starch is first split into dextrin and maltose; the dextrin is subsequently converted into maltose also: this occurs more quickly with erythro-dextrin, which gives a red colour with iodine, than with the other variety of dextrin called achroö-dextrin, which gives no colour with iodine. The following provisional equation is given:—



Ptyalin acts in a similar way, but more slowly, on glycogen: it has no action on cellulose; hence it is inoperative on starch grains, when the cellulose layers are intact. Starches vary appreciably in the ease with which they are digested by saliva. Mere grinding will allow the granules of rice and arrowroot to be acted upon but not so in the case of wheat. It must be remembered that the husk of the seed contains a diastatic enzyme which would assist the saliva were it not commonly removed by milling or destroyed by the processes used in whitening the flour.

Salivary digestion by swallowed saliva continues in the stomach for a variable time. In some cases Cannon found that the food lying in the fundus of the stomach of animals in a quiescent horizontal posture underwent amylolysis for at least two hours, because the relative absence of movement in this region until quite late stages in digestion prevented admixture with gastric juice, especially in the interior of the swallowed masses.

If an animal is fed on different coloured foods it will be seen that the last taken passes into the centre of that which has previously entered. In this way the period of salivary digestion in the stomach is prolonged, since the food moistened with saliva is protected for a time from the gastric juice the acidity of which destroys ptyalin. Recently Campbell and Pembrey have demonstrated that even in man salivary digestion may continue much longer than is commonly supposed; especially is this the case if the secretion of gastric juice has been diminished by severe exercise. It is of interest to observe that normally we take fat with starch (*e.g.* butter with bread, cream with pastry, milk with porridge), and that the effect of fat is to reduce appreciably the amount of gastric secretion and presumably to prolong salivary digestion.

Ptyalin acts best at about the temperature of the body (35-40° C.). For its action, salt ions are necessary, especially the chlorine ion

of sodium chloride as may be seen by the rise of blood sugar after a carbohydrate meal if salt is given. Ptyalin acts best in a neutral or slightly acid medium and in the presence of small amounts of salts; a small amount of alkali makes but little difference; a very small amount of additional acid stops its activity. Starch digestion is eventually stopped by the hydrochloric acid secreted by the glands of the stomach which destroys the ptyalin.

The lubricating and cleansing action of saliva is important in relation to speech and swallowing. Dry food is made into a plastic mass and lubricated by the mucin, while after a meal the saliva does much to prevent food and debris lodging in the teeth. Some claim that its buffering action is an important protection against the acids produced by bacteria which might decalcify the enamel of the teeth. Certainly caries takes place where such lodgment is present. When the saliva is deficient as in fevers the mouth becomes foul and the tongue furred.

The Saliva and Heat Loss.—Much of the difficulty in interpreting the results of stimulation in different animals is due to the fact that saliva is not only a digestive juice but an important substance in maintaining the moisture of the mouth in those animals which depend on heat loss from the respiratory tract, *e.g.* the dog and sheep. In conditions of great fear, *e.g.* during an air-raid, a dog may pant and secrete very large amounts of watery saliva, as it does if it gets too hot.

The Saliva and Water Balance.—As we shall see in a later section the moisture of the mouth determines the sense of thirst which is appreciated by the nerve endings at the back of the tongue. Saliva, therefore, plays an important factor in the maintenance of the water balance of the body. When the blood becomes too concentrated saliva is reduced.

The excretory function of saliva is suggested by the various substances which it may contain, *e.g.* urea in kidney disease, sugar in pancreatic disease, lead in lead poisoning, sulphur and calcium. The latter becomes deposited as tartar on the teeth. Bacteria and viruses are also excreted in some diseases and cause the saliva to become a source of infection.

CHAPTER XXIX

DIGESTION IN THE STOMACH

THE stomach performs a twofold function. It acts as a container of food, a function which is specially important in ruminants which regurgitate the food during the act of rumination. The stomach acts as an organ of digestion by providing facilities for the continuation of salivary digestion and by initiating the digestion of the proteins; this latter it does in virtue of the gastric juice secreted by the glands in its wall.

The Composition of Gastric Juice.

This varies according to the time at which the sample is taken after a meal, but average figures are given in the following table:—

Constituents:—

	Per cent.
1. Water	99·44
2. Enzymes (chiefly pepsin, rennin, lipase)	0·32
3. HCl, free	0·02-0·2
4. Chlorides (inorganic as HCl)	0·03-0·3
5. Phosphates	} about 0·01
6. Organic acids	
7. Blood-forming (hæmopoietic) factor.	
8. Bile which has regurgitated from the duodenum.	
9. Mucus.	
10. Nerve-nourishing (neuropoietic) factor.	

The presence of the specific acid was first recorded by Silliman of Yale in samples from St Martin. The acidity had been noted by Beaumont.

The Hydrochloric Acid.

Of special interest is the HCl and chloride content of the juice, as they have a special relation to gastric ulcer. In practice the free HCl is estimated by titration with N/10 NaOH, using Töpfer's reagent, which changes from red to yellow at pH 3·6, as an indicator, then total chlorides by the Volhard method. The content of inorganic chlorides is then found by subtracting 1 from 2. The total acidity of the juice is estimated, using phenolphthalein, which changes at pH 8·3 from colourless to red, as an indicator, and is of interest, as

this, less the free HCl, gives the amount of organic acid present. It must be understood that the chlorides may be expressed as such or as HCl, but one expression may readily be converted into the other by making use of the molecular weights $58.5 \text{ NaCl} \equiv 36.5 \text{ HCl}$. These simple estimations do not take into consideration HCl in combination with protein. This is really included in the inorganic chlorides as estimated above and in the total acidity.

The normal amount of juice per hour is usually about 200 c.c., of which about 1.85 c.c. is free HCl. The mucus varies very much in amount and appears to act as a lubricant and protective. It is greatly increased by irritants.

The Source of the Hydrochloric Acid.—This acid is produced from the oxyntic cells of the fundus glands. The chloride comes from the blood whose chloride content becomes lowered during secretion, but how living cells can produce such a strong acid is difficult to understand. The probability now appears to be that phosphates play an important part, and that the acid is released according to the reaction $\text{NaH}_2\text{PO}_4 + \text{NaCl} = \text{Na}_2\text{HPO}_4 + \text{HCl}$. HCl is known to be set free in the carriage of CO_2 by the blood. The injection of dyes and staining reactions have suggested that the interior of the cells may really be acid.

In support of this view it has been found by Collip that the parietal cells are very rich in phosphates and poor in chlorides during rest, while the latter rises during activity. Further, it has been shown that circumstances which tend to shift the acid-base equilibrium of the body towards the acid side increase the secretion of HCl, e.g. the administration of CO_2 or acid sodium phosphate.

Actions of Gastric Juice.

The action of gastric juice depends on its content of **Pepsin and Hydrochloric Acid**. These act together in the digestion of protein at an optimum of $\text{pH } 1.5$, i.e. about equal to $\text{N}/10 \text{ HCl}$. Pepsin is an enzyme and may be differentiated from the trypsin of the pancreatic juice (see below) by the fact that it acts in acid solution only. It has now been prepared in crystalline seed-like form, but its exact nature remains undetermined. It is probably a protein. (See Enzymes, p. 304.)

Native proteins are digested by the pepsin-hydrochloric combination into peptones (see Protein Hydrolysis), but the peptone resists further breakdown by this enzyme. The only proteins not digested are the sclero-proteins and protamines.

The digestion of protein envelopes of cells facilitates the digestion of starch and fat by other enzymes, and, therefore, insufficiency of acid may be an important cause of the intestinal fermentation of starch (Knott and Hurst).

Gastric juice, because it digests and destroys bacteria, is **antiseptic**. Many bacteria are swallowed with the food, and thus the body is protected from them. If, however, they are in excessive numbers they may escape digestion and cause putrefaction or disease, such as typhoid fever.

Rennin curdles milk by converting the soluble caseinogen of milk into insoluble casein, which combines with calcium to form calcium caseinate, the curd which is subsequently digested by the HCl and pepsin. Rennin and pepsin are distinct enzymes. They may be precipitated and destroyed by different agencies as their optimum reactions suggest.

The reaction takes place at an optimum pH of 6.0 to 6.5, a fact which facilitates the clotting of milk soon after being taken, since at this pH pepsin is inactive.

Lipase, a fat-splitting enzyme, is present in small amounts. The protein envelopes of the fat-cells are first dissolved by the pepsin-hydrochloric acid, and the solid fats are melted. They are then split in small measure into their constituents, glycerol and fatty acids. This action is mainly produced by a regurgitation of the contents of the duodenum mixed with pancreatic juice; but even after the pylorus has been ligatured and regurgitation prevented, the gastric juice itself produces a *small* amount of fat-splitting, and therefore contains lipase.

Gastric juice **inverts cane-sugar** into glucose and fructose. This also is due to the acid of the juice and is frequently assisted by inverting enzymes contained in the vegetable food swallowed. The juice has no action on starch.

Mucus or mucin is an important protective agent against auto-digestion and is increased greatly by irritants.

It is a slimy, viscid, tenacious substance and probably plays an important part in the protection of the stomach. It is a glycoprotein which has a remarkable antiseptic action due to the mucoitin-sulphuric acid which it contains (Babkin and Komarov). A dried preparation is now used clinically where it is desired to inhibit peptic digestion (*e.g.* in gastric ulcer).

The Blood-forming (Castle's Extrinsic) Factor.—The presence of this factor, as has been indicated in relation to the red blood-corpuscles, was first suspected because of the defective gastric secretion so common in the disease pernicious anæmia, in which there is a great paucity of such corpuscles in the blood. The administration of pig stomach is found to be beneficial in the treatment of the disease, and more especially that part of the duodenum which contains Brunner's glands.

The hæmatinic principle is present in normal gastric juice and is quite distinct from its other constituents, but is destroyed by

heating to 70° C. Its production does not, however, run parallel to the HCl or pepsin. Since normal gastric juice alone is ineffective in benefiting pernicious anaemia but becomes so on being incubated with beef, it is concluded that an intrinsic factor of the juice reacts with an extrinsic principle present in ox muscle, yeast, and other articles of diet to liberate a *haematinic principle* which is stored in the liver, conferring on liver its curative properties in relation to the disease.

The Neuro-poietic Factor.—There is some evidence that the stomach may also produce a substance which is concerned with the nutrition of the nervous system, for the chronic inflammation and atrophy of the organ, which produces pernicious anaemia, is sometimes associated with degeneration of the postero-lateral columns of the spinal cord.

Bile may be present when the stomach is empty and is due to regurgitation of the duodenal contents.

The Limitation of Gastric Acidity.—It is seen that the percentage of HCl in freshly secreted gastric juice is about 0·5 per cent., but it must be understood that this concentration of HCl is not normally in contact with the stomach-wall. During digestion much of the free HCl is neutralised by the amphoteric protein of the food and the ultimate percentage is only about 0·1 to 0·2 per cent., which is about the optimum *pH* 1·5 for the action of pepsin.

When the food has left the stomach the acidity is prevented from rising by regurgitation of the alkaline fluid from the duodenum. The evidence for this is that bile and lipase may be found in the stomach, and that although at the end of an hour and a half after a meal there is a reduction in the concentration of free HCl in the stomach, the chloride content still remains high. This is well seen in fig. 157. Regurgitation has also been observed by X-rays (Bolton). Some neutralisation may also take place as a result of the secretion of alkali by the cells of the pylorus as described by Heidenhain, while Beaumont in his original experiments on Alexis St Martin noted that the mucous membrane was alkaline during rest.

According to Maclean, however, the persistence of the high chloride content is due to the secretion of neutral chloride by the stomach itself, and the fall in the free HCl is due to the action of H-ions on the stomach. In support of this theory he has shown that the introduction of any acid into the stomach will cause a cessation of the secretion of HCl produced by dilute alcohol, but he does not explain why this mechanism so readily breaks down and hyperchlorhydria occurs. The views of Bolton and Maclean are not, however, mutually exclusive.

There is reason to believe that regurgitation from the duodenum is of clinical importance and that if it is reduced and the gastric

acidity rises there is an abnormal liability to gastric ulcer, for the hyperchlorhydria prevents an injury of the mucous membrane from

healing. On the other hand, excessive regurgitation may occur to neutralise abnormal acids (*e.g.* butyric) taken in with or produced from the food, and may result in the so-called "bilious attack."

It has long been stated that the administration of fat increases the regurgitation from the duodenum, but in view of the work of Roberts a more detailed investigation of this problem is necessary.

In this connection it is interesting to note that bile precipitates pepsin.

Variations in the Quality of Juice produced by Different Stimulants.

There has been considerable evidence that the juice produced by different stimulants varies. Meat has been found to produce a juice higher in acid content than that of bread but lower in pepsin content. Even milk causes a slightly greater acidity

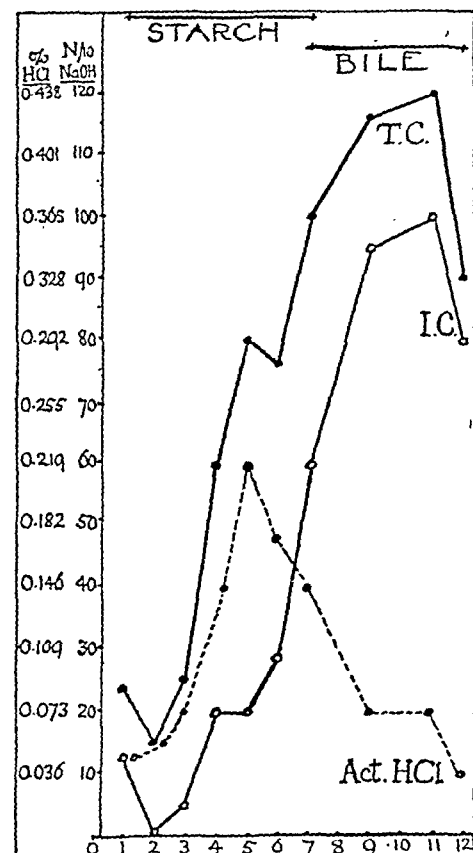


FIG. 157.—A record by Bolton of the analysis of gastric juice of a normal man taken by the fractional method. T.C., Total chlorides; I.C., Inorganic chlorides; Act. HCl, Free hydrochloric acid. Samples were taken each quarter of an hour. Described in text.

than bread but less pepsin (Pavlov, Carlson).

Why does the Stomach not Digest Itself?—There have been many theories advanced to explain this. Claude Bernard suggested that the mucus and the epithelium were protective, others have suggested the alkalinity of the tissues, the presence of anti-enzymes, and the difference between the structure of living and dead tissue. One or more of these factors may play a part, but the latest evidence, of Northrop, indicating that the digestive enzymes do not enter living cells because they cannot pass the cell membrane until the cells are dead, takes us a step further.

The historical aspects of the subjects are given by Robertson, 1931. See also Ryle, 1926.

Methods of Investigating Gastric Secretion.

The early physiologists arrived at the idea of the chemical action of the gastric juice by somewhat heroic methods. We read of Spallanzani (1729-99), originally Professor of Mathematics and Greek at Reggio, who swallowed sponges tied to strings and pulled them up again to obtain samples; of Stevens in Edinburgh (1777), who persuaded a man to swallow small perforated boxes containing meat, which were later regurgitated; and of Lavoisier in Paris, who swallowed linen bags and even perforated boxes filled with meat and examined them after they had been voided per rectum. He also obtained samples of gastric juice by making himself vomit before breakfast, and showed that it brought about digestion *in vitro*.

Fistula.—The most celebrated investigations are those of Beaumont, an American Army surgeon, upon Alexis St Martin in 1822, who, in virtue of a gunshot wound, had a gastric fistula, *i.e.* an opening between the stomach and the exterior. He showed that the taking of food caused a reddening of the gastric mucous membrane and a secretion of hydrochloric acid. Carlson has studied a similar subject (see below).

Fractional Method of Rehfuess.—A rubber tube of small bore (Einhorn) with an expanded end and enclosing a metal bead (Ryle) is used. It may be left in position for several hours if desired. Samples may then be drawn off at intervals of 15 minutes by means of a syringe and the results of analysis expressed on a curve (see fig. 157, p. 418). The test "meal" consists of strained porridge (flavoured with salt) which is readily aspirated, or of dilute alcohol. Some investigators, however, prefer to administer by subcutaneous injection histamine (0.75 mg.) or 15 units of insulin. Histamine (see special section) is, however, liable to cause severe headache and fainting. These tests are now used extensively to determine the functional activity of the stomach, which becomes greatly reduced in inflammatory states of long standing; but it will be realised that semi-solid meals result in a considerable dilution and neutralisation of the juice, and that when the emptying of the stomach is rapid the concentration of acid in the juice rises more rapidly than normally. Swallowed saliva causes both dilution and neutralisation and is to be avoided. It must be admitted that there are so many fallacies in the test and it is so difficult to obtain a state of mental quiet in a patient unaccustomed to the sometimes disagreeable technique, that as a diagnostic aid the test does not give so much information as first thought. The complete absence of HCl is a valuable indication of inflammatory damage to the glands, and a high climbing acidity curve indicates that the subject is liable to ulcer.

The Method of the Pavlov Pouch.—Much of our knowledge has been obtained by the use of the **Pavlov pouch** (so called after its inventor). A piece of the stomach with its nerve and blood supply intact is completely separated off from the main stomach. Such a pouch reacts to various stimuli like the main stomach, although food does not normally enter it. (See fig. 158.)

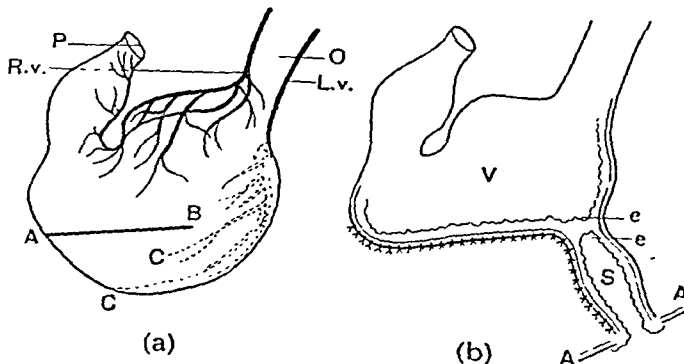


FIG. 158.—*The Pavlov Pouch.*—All the layers of the anterior and posterior walls of the stomach are cut along the line AB. This is parallel to the line of the blood-vessels and avoids the vagus nerves L.v. and R.v. The mucous membrane of the anterior and posterior walls is cut (a) and sewn (b) to form a sac S which is separated by two layers of mucous membrane, e. The muscular and peritoneal coats are then sewn as indicated and the mucous membrane of the sac sewn to the skin of the abdominal wall A with which it rapidly fuses. (From Pavlov.)

Another procedure adopted was to divide the oesophagus and attach the two cut ends to an opening in the neck. The animals could thus be subjected to: (1) real feeding, (2) sham feeding, by allowing them to eat food which subsequently passed out through the neck opening, and (3) psychical feeding, in which the animal was shown the food but was not allowed to eat it.

Mechanism of Secretion of Gastric Juice.

1. *Central Nervous Mechanism.*—As long ago as 1852 Bidder and Schmidt showed in a dog with a gastric fistula that the sight of food caused a secretion of gastric juice; and in 1878 Richet observed that in a man with complete occlusion of the gullet the act of mastication caused a copious flow of gastric juice.

Sham feeding with stones, butter, salt, pepper, mustard, and acid, though it excited a flow of saliva, produced no effect on the stomach. If, however, meat was used for the sham feeding, an abundant and active secretion (**gratification of appetite secretion**) occurred in the stomach (that of the small stomach was actually examined) after a latency of about five minutes. The secretion is thus adapted to

the kind of food the dog has to digest; the larger the proportion of protein in the diet, the more abundant is the juice, and the richer both in pepsin and acid.

Indeed, if the animal is hungry and shown the meat and not allowed to swallow it, the effect is almost as great (**psychical secretion**), but if the animal is not hungry, secretion may be practically absent. The following striking experiment also shows the importance of the psychical element. Two dogs were taken, and a weighed amount of protein introduced into the main stomach of each without their knowledge; one was then sham fed on meat, and one and a half hours later the amount of protein digested by this dog was five times greater than that which was digested by the other. The efferent pathway concerned is probably the vagus, as the following experiments suggest.

If the vagi are cut (below the origin of the recurrent laryngeal to avoid paralysis of the larynx), and sham feeding is then performed with meat, no secretion is obtained; the vagi therefore contain the secretory fibres. The experiment of stimulating the peripheral end of the cut nerve confirmed this hypothesis. The nerve was cut in the neck four or five days before it was stimulated; in this time degeneration of the cardio-inhibitory fibres took place, so that stoppage of the heart did not occur when the nerve was stimulated; under these conditions a secretion was obtained with a long latency; the latency is explained by the presence of secreto-inhibitory fibres. Atropine abolishes this action of the vagus as it does all secretions. The removal of the cerebral cortex also abolishes this vagal secretion from the smell and sight of food, *i.e.* psychical secretion. It does not, however, abolish gratification of appetite secretions which depend on the more direct stimulation of taste.

The juice produced when the vagus is stimulated is rich in both pepsin and HCl, and during its secretion the vessels of the stomach wall become engorged with blood. Presumably the vagus brings about a release of acetylcholine at its endings, and possibly histamine also (Babkin).

Stimulation of the sympathetic causes a secretion of a poor digestive quality but rich in mucus. It seems probable that the erosions of the stomach which are produced by damage to the hypothalamus of the brain are due to lack of sympathetic activity and of mucus.

The Effect of Insulin.—Gastric secretion is brought about by the injection of insulin. The cessation of the secretion when glucose is injected into the blood stream indicates that the secretion is due to the fall of the blood glucose which insulin brings about, but the effect is not direct for it is found that reduction of the glucose in the blood to the brain only has a similar result. The nervous

pathways concerned appear to be the vagi, for the secretion is rich in pepsin and is abolished if the nerves are cut. For some unexplained reason there is, however, sometimes an interval of almost an hour before the secretion appears.

Parathyroid extract also causes a secretion of gastric juice.

2. *Gastric Mechanisms.*—These factors in digestion are studied by putting substances into the stomach without the knowledge of the subject. The mere distension of the stomach with food causes a secretion of gastric juice even when the organ is denervated. How far this is mechanical and the result of the gastric movements set up (Babkin) and how far it is chemical is not quite settled. It is probably both. Certain substances have a special stimulating action on secretion. Of these the most important are meat extracts, but even water may cause a small secretion. Dextrin, a product of salivary digestion, however, as shown by Herzen, causes secretion of much juice rich in pepsin and hydrochloric acid. The products of proteolysis are also peptogenic, so that when once digestion has started, a stimulus for more secretion is provided.

Alkalis such as sodium bicarbonate, except in large doses, cause a secretion of gastric juice, but neutralise it at first, while acids such as acetic bring about a cessation of acid secretion (Maclean).

It has recently been denied that substances like meat extracts or alkalis produce these effects by local action (Babkin, Ivy). In man, of course, psychic and appetite effects are not usually excluded. Histamine causes a marked secretion.

It was found by Edkins that extracts of the wall of the pyloric canal injected into the blood stream caused a secretion of gastric juice, and he suggested that the hydrochloric acid in coming in contact with the pyloric canal causes the absorption into the blood of a substance *gastrin*, which causes this gastric secretion. Several workers, especially in America, in attempting to repeat these observations have, however, concluded that the stimulating principle is really histamine (Gavin, McHenry, and Wilson) but Lim of Pekin has been equally satisfied that histamine-free extracts are effective. This latter view receives some support. Ivy and Farrell have succeeded in transplanting a pocket of stomach to the mammary region and have found that digestion in the stomach led to a secretion in the pocket. Ivy and other collaborators could not, however, prepare active extracts free from histamine.

Certain articles of diet such as fat diminish the gastric secretion during the first hour but thereafter the acidity of the gastric juice may be increased, possibly owing to delayed emptying and to absence of duodenal regurgitation (Roberts). If, therefore, fats are given to reduce secretion it is essential that they are followed later by alkali such as magnesium oxide. According to Ivy, the fat brings

about the release of an inhibitory agent *enterogastrone* from the intestine which acts by way of the blood stream.

3. *Intestinal Mechanisms*.—It has now become evident that the presence of food in the intestine causes a secretion of gastric juice. It occurs after section of all nerves, but how exactly it is produced is not quite certain. A hormone may be produced or the products of digestion after absorption may stimulate (Lim, Ivy, McCorky).

Carlson's Man.—A large amount of information regarding the secretion of gastric juice in man has been obtained by Carlson in a man with a gastric fistula like that of Alexis St Martin. He has shown that, apparently, the psychic secretion is not so important in man as the experiments of Pavlov suggest, but that the secretion which takes place when there is gratification of appetite is specially important. Apparently man, being more sophisticated than the dog, does not unconsciously presume he will get food until he actually does so. Carlson has shown that articles which are pleasant to the taste of the individual, evoke considerably more gastric juice than others. We see here the importance of the cook in relation to our digestion. Whatever the actual cause there can be no doubt that meat extracts, especially if pleasantly flavoured, cause a marked increase in the hydrochloric acid and pepsin in normal man, a point of very considerable importance in the stimulating of poor digestion and conversely in the prevention of excessive secretion in the treatment of gastric ulcer.

The **effect of emotion** on gastric secretion has been clearly demonstrated. It was noted in Pavlov's laboratory that the sight of a cat markedly reduced the amount of juice secreted by a dog, and other similar observations have been made in Carlson's man, and also by Venables and Bennett, who have shown that, as in the case of the saliva, the secretion of gastric juice may be markedly reduced by mental stress. They hypnotised an airman with a gastric tube in position and found that there was an immediate reduction of gastric secretion when flying difficulty was suggested to him. It has also been shown that sympathetic stimulation causes a reduction of gastric secretion (Flint and Moll). We shall see later that gastric movements may similarly be reduced. Disgusting smells such as that of indole also inhibit secretion (Hawk).

The Physiological Order of a Dinner.—It is of considerable interest that mankind has gradually evolved an order of taking articles of food which is fairly physiological. The tasty *hors-d'œuvre* or soup come early to stimulate secretion, in virtue of appetite secretion and of the effect of meat extracts. This is followed by the main protein course. Then comes the carbohydrate or sweet course, the starch, which by coming late, has all the more chance of being digested by the saliva. Last comes the fruit, which cleanses the

teeth, and whose acid promotes the secretion of saliva for furthering the digestion of the sweet. In addition, as pointed out by Pavlov, we have cultivated the convention that it is a pleasure for individuals to dine together under conditions most favourable for stimulating the appetite and promoting a sense of well-being.

Alcohol.—The consumption of alcohol with meals is a time-honoured custom. It used to be taught that this substance had no stimulating action on the gastric secretion, but since the introduction of the fractional method of investigating the gastric contents it has been found that *dilute* alcohol causes a very appreciable secretion of hydrochloric acid (Maclean). There seems little doubt, also, that by paralysing some of the higher mental mechanisms it promotes a sense of well-being and by “drowning” cares may be of much value in promoting digestion.

The Effect of Exercise.—There is now some evidence that physical exercise may bring about a secretion of gastric juice. This is suggested by the fact that in anæsthetised animals there is a secretion of gastric juice when the limbs are tetanised (Feldberg). The evidence is that the substance carried in the blood is histamine. The subject is of special interest, as it is known that gastric ulcer, which is aggravated by the acid juice of the stomach, is greatly benefited by physical rest in bed.

On the other hand, in animals with a Pavlov pouch, and also in man, there is evidence that digestion is markedly reduced by severe exercise during or immediately after a meal.

The Structure of the Stomach in Relation to its Function.

The coats of the stomach are similar to those seen elsewhere in the alimentary canal. Especially in the cardiac region it has oblique muscle in its wall.

The glands of the mucous membrane are of three varieties: (a) Cardiac, (b) Fundus and body, and (c) Pyloric.

(a) *Cardiac* glands are (1) simple tubular glands lined by short columnar granular cells, (2) small tubulo-racemose glands, only found quite close to the cardiac orifice. They probably secrete mucus.

(b) *Fundus* and body glands are found throughout the remainder of the stomach except the pylorus. They are arranged in groups of four or five which are separated by a fine connective tissue. Several tubules open into one duct, which forms about a third of the whole length of the tube and opens on the surface. The ducts are lined with columnar epithelium. The gland-tubules are lined with coarsely granular polyhedral cells (*central cells*). The central cells are mingled with a variable number of cells with clearer protoplasm which Lim

proposes should be called *mucoid cells*. Between these cells and the basement-membrane of the tubes are large oval or spherical cells, opaque or granular in appearance, with oval nuclei, bulging out the basement-membrane; these cells are called *oxyntic* or *parietal cells*. They do not form a continuous layer.

The central cells elaborate the pepsinogen granules which may be dissolved out of the wall of the stomach in alkali solution (Langley). Such a solution is not, however, active until made acid and preferably pepsin added.

During secretion they discharge their granules, those which remain being chiefly situated near the lumen, leaving in each cell a clear outer zone. The rennet-enzyme that causes the curdling of milk is also formed by the central cells.

The oxyntic cells undergo merely a change of size during secretion, being at first somewhat enlarged, and after secretion they are somewhat shrunk. They are so called because they secrete the hydrochloric acid of the juice.

(c) *Pyloric Glands*.—These are found in the pyloric canal, and have longer ducts than the fundus glands. Into each duct two or three tubules open by very short and narrow necks, and the body of each tubule is branched and convoluted. The lumen is large. The ducts are lined with columnar epithelium, and the tubules with shorter and finely granular cubical cells, not at all unlike the mucoid cells of the fundus glands. The pyloric glands have no parietal cells. As they approach the duodenum the pyloric glands become larger, more convoluted and more deeply situated. They are directly continuous with Brunner's glands in the duodenum.

These glands secrete a viscid alkaline juice containing no pepsin (Lim).

The function of the various glands of the stomach was originally shown by Heidenhain who succeeded in making, in a dog, culs-de-sac of various parts of the organ.

REFERENCE.—Babkin, 1928.

CHAPTER XXX

DIGESTION IN THE INTESTINES

DIGESTION in the intestine is brought about by the juice which is poured into the gut by the neighbouring gland, the pancreas, assisted by the bile and the secretions elaborated by the glands in the intestinal wall itself.

The Pancreas.

The pancreas or stomach sweet-bread lies in the loop of the duodenum. Generally it resembles the salivary glands in structure, but scattered between the ordinary glandular cells are small masses of epithelial cells free from ducts. These are the **islets of Langerhans** which produce insulin. The granules of the cells are of two kinds: (*a*) granules which are fixed by alcohol, and (*b*) granules which are fixed by fixatives in watery solution, *e.g.* formaldehyde. The granules may be demonstrated by injecting neutral red into the animal before death (*i.e.* intravital staining).

Composition and Action of Pancreatic Juice.

The pancreatic juice may be obtained by a fistula in animals, a cannula being inserted into the main pancreatic duct; but as with gastric juice, experiments on the pancreatic secretion are frequently performed with an artificial juice made by mixing a weak alkaline solution (1 per cent. sodium carbonate) with an extract of pancreas which is usually made with glycerol.

Quantitative analysis of human pancreatic juice gives the following results:—

Water	97.6 per cent.
Organic solids	1.8 „
Inorganic salts	0.6 „

In the dog the amount of solids is much greater.

The organic substances in pancreatic juice are—

(*a*) Enzymes. These are the most important both quantitatively and functionally. They are six in number:—

i. Trypsin, a proteolytic or proteoclastic enzyme. In the fresh juice, however, this is present in the form of trypsinogen, which is less active, but which becomes activated by the succus entericus

ii. and iii. Chymotrypsin and carboxypeptidase which act like trypsin. (Northrop.)

iv. Amylase, an amylolytic (amylolytic) enzyme.

v. Lipase, a fat-splitting or lipolytic (lipolytic) enzyme.

vi. A milk-curdling enzyme.

(b) A small amount of protein matter, coagulable by heat.

(c) Traces of leucine, tyrosine, xanthine, and soaps.

The inorganic substances in pancreatic juice are—

Sodium chloride, which is the most abundant, and smaller quantities of potassium chloride, and phosphates of sodium, calcium, and magnesium. The alkalinity of the juice is due to phosphates and bicarbonates, especially of sodium.

1. **Trypsin.**—The name is derived from a Greek word meaning “to grind.” Thus we are reminded of old views of how the digestion took place. Trypsin acts like pepsin, but with certain differences, which are as follows:—

(a) It acts in an alkaline medium (optimum pH 8.1), (*cf.* pepsin in an acid), but it decomposes rapidly if allowed to stand in solutions more acid than pH 6.0.

(b) It acts more rapidly than pepsin; deutero-proteoses can be detected as intermediate products in the formation of peptone; the primary proteoses have not been detected.

(c) Alkali-meta-protein is formed in place of the acid-meta-protein of gastric digestion.

(d) It acts more powerfully on certain proteins (such as elastin) which are difficult of digestion in gastric juice. It does not, however, digest collagen.

(e) Acting on solid proteins such as fibrin, it eats them away from the surface to the interior; there is no preliminary swelling as in gastric digestion.

(f) Trypsin acts further than pepsin, and rapidly splits up the proteose and peptone which have left the stomach into simpler substances, the polypeptides. The polypeptides in their turn are resolved into their constituent amino-acids. These no longer give the biuret reaction. In addition to these there is a certain amount of ammonia.

Trypsin is then a much more powerful, rapid, and complete catalyst than pepsin, but it acts much more readily after pepsin has already acted on a protein.

Fresh trypsin, or rather trypsinogen, obtained from the pancreatic duct is much less active than trypsin. Activation is brought about by the intestinal juice.

Both trypsin and trypsinogen have now been obtained in crystalline form. The crystals of trypsin take the form of short rods. Those of trypsinogen are in small triangular prisms. (Northrop.)

2. **Chymotrypsin** is an enzyme similar in its action to trypsin but having a different crystalline form and differing in some of its chemical properties. It is activated from its zymogen only by trypsin.

3. **Carboxypeptidase** is present in extracts of pancreas and is probably present also in the secreted juice. Its crystals are larger and less uniform than those of trypsin. It is activated by trypsin and by the enterokinase of the intestinal juice and is proteolytic.

Antitrypsin, etc.—It has also been shown that there exists in the pancreas a trypsin-inhibitor which can be crystallised in hexagonal many-faced crystals.

At this point it is convenient to remark that there is a trypsin-like enzyme in the white blood-corpuscles which digest bacteria.

4. **Amylase (and Maltase).**—Pancreatic juice is much more active than saliva, and it will act even on unboiled starch. The small amount of this enzyme in the juice of infants is an indication that starch is not their natural diet. Some observers have found small quantities of maltase in pancreatic juice.

It has been pointed out by Hurst and Knott that vegetable starches are more easily digested if they are first acted upon by the hydrochloric acid of the stomach. If the starch is not adequately digested it may ferment in the intestine and give rise to flatulence.

5. **Lipase.**—Fats are split by pancreatic lipase into glycerol and fatty acids. The fatty acids unite with the alkalies to form a small amount of soap.

If a glycerol extract of pancreas is filtered, the filtrate has no lipoclastic action; the material deposited on the filter is also inactive, but on mixing it with the inactive filtrate once more, a strongly lipoclastic material is obtained. In this way lipase is separable into two fractions: the material on the filter is inactive lipase; the material in the filtrate is its co-enzyme; the latter is not destroyed by boiling. Bile salts also activate the inactive lipase, and this explains the fact that bile favours fat-splitting.

Pancreatic juice also assists in the emulsification of fats; this it is able to do because it is alkaline, and it is capable of liberating fatty acids, which form soaps with the alkali present; the soap forming a film on the outer surface of each of the fat globules prevents them running together. Such emulsification is, as we shall see, greatly facilitated by the action of bile which reduces surface tension. The proteins present make the emulsions more permanent.

6. **Milk-curdling Enzyme.**—The addition of pancreatic extracts or pancreatic juice to milk causes clotting; but this action (which differs in some particulars from the clotting caused by rennet) can

hardly ever be called into play, as the milk upon which the juice has to act has been already curdled by the rennin of the stomach.*

The Mechanism of Pancreatic Secretion.

It was first shown by Popielski and Wertheimer and Le Page that a flow of pancreatic juice still occurs when the nerves supplying the duodenum and pancreas have been cut through; and later Wertheimer found that the flow can be excited by injection of acid into the jejunum, but not when it is injected into the lower part of the ileum. These authors concluded that the secretion depended on a local reflex.

This subject was reinvestigated by Starling and Bayliss. They showed that the secretion cannot be reflex, since it occurs after extirpation of the coeliac plexus, and destruction of all nerves passing to an isolated loop of intestine. It must therefore be due to direct stimulation of the pancreatic cells, by a substance or substances conveyed to the gland from the bowel by the blood-stream.

Such a substance was discovered by Bayliss and Starling, and called **secretin**. They found that if dilute hydrochloric acid (0.4 per cent.) is placed in the duodenum, or if an extract of the duodenal wall (made with dilute HCl but subsequently neutralised and freed from protein) is injected into the blood-stream, pancreatic secretion occurs, although this is not caused by injection of acid only into the blood-stream. The presence of this acid in the stomach suggested that hydrochloric had a specific action in this way, but subsequently it has been shown (Mellanby; also Harper and Vass) that many substances (food, water, normal saline, alcohol), especially *bile*, when introduced into the duodenum were capable of exciting a flow of pancreatic juice and increased enzyme output independently of nerves. Further, it was recognised from clinical reference that pancreatic digestion was not impaired in the absence of free hydrochloric acid in the gastric juice. An analysis of these and many other factors showed that secretin is present as such in the duodenal mucous membrane, and that secretin is carried into the blood by bile salts when bile is absorbed from the duodenum. Hence the secretion of pancreatic juice is intimately related to the entrance of bile into the duodenum. The discharge of bile from the gall-bladder and liver into the duodenum is in turn determined by the passage of peristaltic waves from the pylorus down the small intestine. Each peristaltic wave is preceded by a wave of inhibition which releases the sphincter of the common bile-duct as it passes through the muscle of the duodenum; this

* Whether the action on milk is due to a special enzyme, or is a side action of trypsin, is a moot point, similar to that raised in relation to pepsin.

relaxation determines the discharge of a few drops of bile into the duodenum. Hence the sequence of events leading to pancreatic secretion is as follows: the stomach discharges its contents into the upper part of the duodenum; this initiates peristaltic waves which pass down the small intestine; when a peristaltic wave reaches the entrance of the common bile duct, the sphincter is relaxed and bile enters the duodenum; the bile salts are absorbed and carry secretin into the blood; the secretin stimulates the pancreas to secrete pancreatic juice and the bile salts are returned to the liver to act as cholagogues.

Secretin has been prepared by Mellanby and appears to be a polypeptide. It is intensely active, 0.03 mgr. injected intravenously into a cat producing about 3.0 c.c. of pancreatic juice. It is soluble in water and dilute alkali, but is insoluble in dilute acid. It is probably the same substance in all animals and is not specific to any one kind of animal. The amount present in the intestinal wall becomes less and less below the duodenum. (See Stile, 1931.)

Although secretin is a special hormone for the pancreas it must be understood that the organ may be stimulated by non-specific substances, such as histamine, which occur in extracts of almost any organ. Secretin causes a copious flow of a dilute solution of sodium bicarbonate from the gland. It also causes the intestinal muscle to contract forcibly.

Another hormone, **pancreozymin**, has been found to be responsible for stimulating the secretion of enzymes by the organ (Harper and Raper). It is found with secretin in alcoholic extracts of the intestine, but the secretin may be removed by dissolving it in bile salt solution, after which the pancreozymin may be precipitated by the addition of NaCl. The substance is thermostable but is destroyed by pancreatic juice. The response of the pancreas to pancreozymin is not affected by nerve section or the administration of atropine.

Pavlov by experiments of a similar nature to those which led him to the discovery of the secretory nerves of the gastric mucous membrane, discovered the secretory nerves of the pancreas in the **vagus**. Later it was shown that the formation of the enzymes of the pancreas is under the control of the vagus nerves. This latter action, as shown by Bayliss and Starling, does not appear to be paralysed by atropine. Secretion is inhibited by stimulation of the sympathetic in the cat (Harper and Vass), but in the dog Pavlov obtained a small secretion by such stimulation.

In concluding, therefore, we may say that the vagus and pancreozymin are responsible for the production of enzymes and that they are carried into the duodenum by the flow of sodium bicarbonate solution caused by secretin, thereby ensuring the presence of the optimum reaction at which the enzymes will act.

Adaptation of the Pancreas.—To a certain degree it cannot be doubted that the pancreas adapts its secretion to the work it has to do. Thus, whereas gastric juice has a maximal flow soon after the ingestion of food, the pancreatic flow does not attain its full force until some time later, that is, when it is wanted. The view that this is due to the hormone named secretin, which is not formed until the gastric contents enter the intestine, fully explains the reason for the delay.

But Pavlov went further than this, and stated that the proportion of the various enzymes of the juice was adapted to the proportions of proteins, carbohydrates, and fats in the food taken. Considerable doubt has been cast on these results, because of the failure to confirm one of the most remarkable instances of such adaptation; this is the power of the pancreas to secrete *lactase* (an enzyme capable of hydrolysing lactose). Normal pancreatic juice contains no lactase, but certain observers stated that by feeding an animal on milk, the pancreas could be educated to secrete it. Careful experiments by Plimmer have shown this is not really so, and therefore much more stringent experimental conditions will have to be imposed before the other adaptations can be considered proven.

The Succus Entericus.

The succus entericus is secreted chiefly by Lieberkühn's crypts. It may be studied in isolated loops. Thiry's method is to cut the intestine across in two places; the loop so cut is still supplied with blood and nerves, as its mesentery is intact; this loop is emptied, one end is sewn up, and the other stitched to the abdominal wound. The continuity of the remainder of the intestine is restored by fastening together the upper and lower portions of the bowel from which the loop has been removed. In Vella's method both ends of the loop are sutured to the wound in the abdomen. (See fig. 159.)

The succus entericus contains an important activator of the pancreatic juice known as **enterokinase**. Claude Bernard, in studying the juice from the pancreatic duct, entirely missed its tryptic action, for the fresh juice is inactive. Later it was shown by Pavlov that if fresh pancreatic and intestinal juices are mixed together, the result is a powerful proteolytic mixture, though neither juice by itself is so active.

Some activation takes place slowly through the influence of calcium (Mellanby and Woolley).

Trypsinogen, the precursor of trypsin, will digest peptones, histones, and protamines, but in association with the intestinal juice will also digest the more resistant substances such as fibrin, gelatin, and casein. (Willstätter, 1928.) It used to be considered that trypsinogen was quite inactive, but this statement refers to its action on certain proteins only.

It was formerly difficult to be sure that the action of trypsinogen was not in part due to a minute amount of trypsin, but now they have been shown to be quite distinct by crystallisation.

Several suggestions have been made as to how **activation** may take place. It may be that trypsinogen is a complex consisting of trypsin united with a protein moiety, and so long as the enzyme is combined

in this way it is only partially active; enterokinase acts upon the protein moiety, and thus liberates the trypsin (J. Mellanby and Woolley). In any case it seems certain that the activation is due to the rupture of a peptide link (Northrop).

Trypsinogen, however, does not depend wholly on enterokinase for activation. It may become spontaneously activated in ground-up pancreas or be transformed into trypsin by auto-catalytic action at pH 7.0.

It is also suggested (Waldschmidt-Leitz) that the trypsin action is restricted to the splitting of two arginine groups, since it needs neither NH_2 nor COOH groups. This is shown by the fact that it still acts if H is added to the NH_2 or if the COOH group is esterified. Some protein-splitting enzymes need these groups. Enterokinase

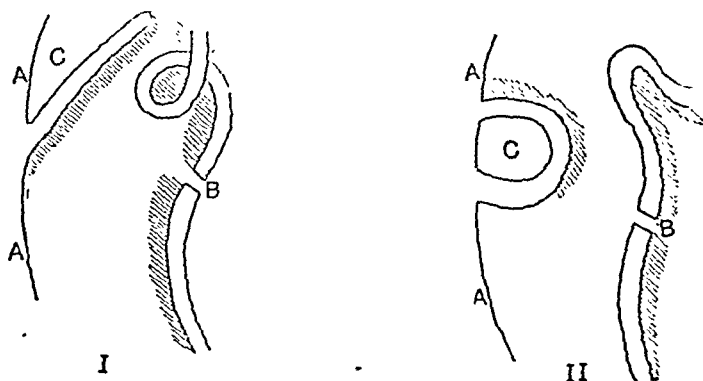


FIG. 159.—Diagram of intestinal fistula. I, Thiry's method; II, Vella's method. A, Abdominal wall; B, intestine, with mesentery; C, separated loop of intestine, with attached mesentery.

appears to be one of these. This may explain why it has been found that enterokinase appears to enter into chemical combination with trypsinogen in definite proportions. It may really be a combination with substrate acted upon by trypsinogen. Enterokinase is therefore not an enzyme as its name suggests, or it may be that eventually all enzymes will be shown to act similarly.

Succus entericus has no action on native proteins such as fibrin and egg-white, but it acts on proteoses and peptone (Cohnheim). It rapidly breaks them up into simpler substances, of which ammonia, leucine, tyrosine, and the hexone bases have been identified. Cohnheim named the enzyme to which this is due **erepsin**. Hamburger found that erepsin is also present in the human juice; it is not identical with enterokinase, because erepsin is destroyed by heating the juice to 59°C . for three hours; enterokinase is not destroyed until the temperature is raised to 67°C . A similar enzyme is present in most tissues; it is most abundant in the kidney. (Vernon.)

Cohnheim investigated the action of erepsin on a large number

of proteins; it acts energetically on proteoses, peptone, and protamines: on histones, which occupy an intermediate place between protamines and the other proteins, it has a slight action. On the other native proteins it has no action, with the single exception of caseinogen, which is speedily broken up into simple substances; this opens up the interesting physiological possibility that the suckling infant is able to digest its protein nutriment even if pepsin and trypsin are absent.

The succus entericus possesses the power of converting disaccharides into monosaccharides. This power it owes to three enzymes. **Invertase** or *sucrase* is the enzyme which inverts and hydrolyses sucrose or cane-sugar—that is, it converts sucrose into glucose and fructose. The chemical term “inversion” has already been explained. It has been extended to include the similar hydrolysis of other disaccharides, although there may be no formation of lævotatory substances. The enzyme in the juice which converts maltose into glucose is called **maltase**; and that which acts upon lactose is called **lactase**. It also contains nucleinase, phosphatase, and deaminase, which act as their names suggest.

The secretion of the intestinal juice is brought about by the presence of the intestinal contents which cause mechanical and also chemical stimulation. The various products of digestion such as dextrans, soaps and proteoses are particularly efficient excitants if placed in isolated intestinal loops. Secretin and histamine, if injected into the blood-stream, cause a marked secretion; indeed if secretin is administered to a fasting animal, the mixture of pancreatic and intestinal juice secreted is so powerful, that having no food to act upon, it will produce inflammation and erosion of the intestinal wall. (Starling.)

The presence of pancreatic juice causes the intestine to secrete enterokinase.

The **bile**, as we shall find, has little or no digestive action by itself, but combined with pancreatic juice it assists the latter in all its actions. This is true for the digestion of starch and of protein, but most markedly so for the digestion of fat.

Bile has also an important action in stimulating pancreatic secretion and in the absorption of fats. Occlusion of the bile-duct by a gall-stone or by inflammation prevents bile entering the duodenum. Under these conditions the faeces contain a large amount of undigested and digested fat which has escaped absorption.

General Aspects of Digestion.

In our consideration of digestion we see that the occurrences in the alimentary canal are not a series of isolated phenomena. Each

step follows in an orderly manner as the result of the previous one. The product of salivary digestion, dextrin, causes gastric secretion; both secretions are affected by mental states which also affect gastric movements. The food leaving the stomach sets up peristaltic waves in the duodenum and causes the pouring out of bile which in turn causes the absorption of secretin from the duodenal wall; the secretin is taken by the blood-stream to the pancreas, where it excites a flow of pancreatic juice; this juice arrives in the duodenum ready to act on starchy substances and on fat. The pancreatic juice, however, cannot act on proteins without enterokinase, which is supplied by the succus entericus; this activates the trypsin. The trypsin and alkali with the assistance of erepsin effectively complete the proteolysis begun by the acid and pepsin of the stomach, while the inverting enzymes of the succus entericus complete the digestion of the carbohydrates.

The rôle of hormones in the process of digestion generally is discussed by Ivy, 1930, and the mechanism of secretion by the stomach by Babkin, 1933. The early work on the subject of the digestive glands is given by Pavlov, 1902.

CHAPTER XXXI

SOME METHODS USED IN INVESTIGATING DIGESTIVE JUICES

The following are important examples of methods commonly used:—

To estimate Amylolytic Activity.—The most typical of numerous methods employed in the investigation of the rate of starch digestion (by saliva, pancreatic amylase, plant diastase, etc.) consists in the determination of the *achromic point*, that is, the moment when iodine ceases to give a colour, all the erythro-dextrin having been converted into achroö-dextrin and maltose. The mixture of starch solution and digestive fluid in known proportions is kept in a water-bath at constant temperature ($40^{\circ}\text{C}.$). Every half minute or so a drop of the mixture is transferred with a glass rod to a drop of iodine solution on a testing slab. As long as starch is present the colour struck will be blue; then as erythro-dextrin appears the colour will be violet, and when all starch has gone, reddish-brown. This gradually gets fainter and fainter until finally the achromic point is reached. The time occupied from the start is noted. If this is done with the same quantity of saliva from different people a relative measure of the activity of their saliva is obtained. If it is done with different quantities of saliva from the same person, it will be found that the time occupied in reaching the achromic point is inversely proportional to the amount of saliva used.

To estimate Activity of Lipase.—As before the digestive fluid containing the enzyme is mixed with the fat, and after incubation at the usual temperature for a given time, the amount of fatty acid liberated can be ascertained by titrating with a standard solution of alkali using phenolphthalein as indicator, the point of neutrality with this indicator being signalled by the appearance of a pink colour.

To estimate Proteolytic Activity.—Here the methods are numerous, and may be divided into two categories: (*a*) those in which the rate of solution of a solid protein is used as an index of the action of the enzyme, as in Roaf's and Mett's methods, and (*b*) more complex methods in which the rate of action is ascertained by estimating the amount of the products (amino-acids) liberated.

Roaf's Method.—This is a modification of Grützner's method. Grützner used fibrin stained with carmine, and when the fibrin is digested the carmine is set free, and from the depth of colour of the liquid the amount of fibrin digested can be estimated colorimetrically. The disadvantage of this method is that it can be used only for gastric juice, since when alkali is present the carmine is dissolved out by it before digestion sets in. This was overcome by Roaf by using Congo-red instead of carmine.

Mett's Method.—This is now very generally employed. Pieces of narrow glass-tubing of known length are filled with white of egg. This is set into a solid by heating to 95°C . The tubes are then placed in the digestive fluid at 36°C ., and the coagulated egg-white is digested. After a given time the tubes are removed; and if the digestive process has not gone too far, only a part of the little column of coagulated protein will have disappeared; the length of the remaining column is easily measured, and the length that has been digested is a measure of the digestive strength of the fluid.

The Formaldehyde Method of Sørensen.—In this method the basic amino-groups liberated are methylated by the addition of formaldehyde, with the result that the digestion mixture becomes more acid. The progress of the reaction, indicated by increasing acidity, can be followed by titrating with $\frac{N}{10}$ NaOH. The usual procedure is to place the digestion mixture of protein, trypsin, and 0.4 per cent. sodium carbonate in an incubator at 37° – 40°C ., to withdraw samples every fifteen minutes, neutralise, add formalin, and titrate. The results can be shown graphically.

Colour Tests for Gastric Acids.—*Hydrochloric acid* is absent in some diseases of the stomach, notably in cancer; many colour tests for this acid have been introduced from time to time, but by far the most characteristic and delicate is the following:—

Töpfer's test.—A drop of dimethyl-amino-azo-benzene is spread in a thin film on a white plate. A drop of dilute hydrochloric acid (up to 1 in 10,000) strikes with this in the cold a bright red colour.

Lactic acid is soluble in ether, and is generally detected by making an ethereal extract of the stomach contents, and evaporating the ether. If lactic acid is present in the residue it may be identified by using a ferric chloride-phenol solution made as follows:—

10 c.c. of a 4-per-cent. solution of phenol.

20 c.c. of distilled water.

1 drop of the liquor ferri perchloridi of the British Pharmacopœia.

On mixing a solution containing a mere trace (up to 1 part in 10,000) of lactic acid with this violet solution, it is instantly turned yellow. Larger percentages of other acids (for instance, more than 0.2 per cent. of hydrochloric acid) are necessary to decolorise the test solution, but they do not turn the solution yellow.

Another colour test, that of Hopkins, is performed as follows:—5 c.c. of sulphuric acid and 3 drops of a saturated solution of copper sulphate are added to a few drops of lactic acid dissolved in alcohol. The mixture is placed in boiling water for five minutes, and then cooled; 2 drops of 0.2 per cent. alcoholic solution of thiophene are then added; on replacing the tube in boiling water a cherry-red colour develops.

CHAPTER XXXII

THE ABSORPTION OF FOOD

Food is digested in order that it may be absorbed. It is absorbed in order that it may be assimilated, that is, become an integral part of the living material of the body. The digested food thus diminishes in quantity as it passes along the alimentary canal, and the faeces contain the undigested or indigestible residue.

Foods such as water and soluble salts like sodium chloride are absorbed unchanged. The organic foods are, however, considerably changed, colloid materials such as starch and protein being converted respectively into the diffusible materials glucose and amino-acids.

We have seen that the structure of the alimentary canal is peculiarly adapted to its various functions.

In the mouth and oesophagus the thickness of the epithelium and the quick passage of the food through these parts reduce absorption to a minimum. Absorption takes place very slightly in the stomach. The most recent observations show that water is not absorbed in the stomach, but alcohol is absorbed to some extent, and also prussic acid. Water, indeed, may invoke a secretion of gastric juice. Salts also do not seem to be absorbed unless present in great concentrations, such as do not occur in normal diets; sugar is absorbed with difficulty.

Absorption takes place particularly in the upper part of the small intestine, and by the time the intestinal contents reach its lower end the products of digestion have been largely absorbed. In the large intestine water particularly is absorbed.

There are two channels of absorption, the blood-vessels (portal tributaries) and the lymphatic vessels or lacteals. In general terms, the proteins and carbohydrates and some fats are absorbed by the blood-vessels, and the rest of the fats by the lacteals.

This formation of water-soluble, diffusible substances is not, however, the only significance of the breaking down of foodstuffs. It is *also* essential that these breakdown products should be *non-specific substances*. The importance of this can be seen with proteins. Proteins of one species of animal are toxic if injected into the circulation of another species, and cause the production of specific antibodies. But if the same protein is taken into the intestine, it is split up into non-specific and non-toxic amino-acids (or polypeptides).

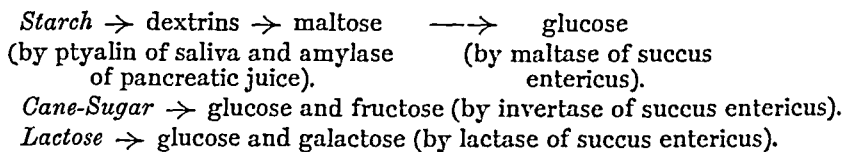
Such a destroying of the toxicity probably also occurs during the absorption of fats. Fatty acids would be toxic if absorbed in very large amounts, and the resynthesis to neutral fat abolishes this danger.

A third significance of the breaking down of foodstuffs is closely related to the above. The body builds up from its food, tissues which are specific to the animal, and this is only possible if the food substances are first broken down to relatively simple molecules. The different plant and animal proteins which are eaten are broken down and built up again into the proteins which are specific to the species. Similarly, fats are split up into different fatty acids, which, after absorption, combine with glycerol to form the specific fats of the animal, with characteristic composition in the different organs. This formation of specific fats can, however, be influenced by the nature of the fatty acids in the food. If excessive quantities of a certain fat are fed, the nature of the fat of the reserve deposits will be altered. When such reserve fat is needed in metabolism, however, it changes into the normal specific fat before passing to the organs.

Among the carbohydrates the disaccharides (sucrose, maltose and lactose) are diffusible and can be absorbed as such, but are then passed through the body to a great extent unused. Normally, however, when not present in very great quantities, they are broken down into monosaccharides, which can be used as such by the body, or built up into glycogen, the characteristic polysaccharide of animals.

Thus, in the intestine, the foodstuffs are converted into forms which are not only *diffusible*, but also *non-toxic*, and capable of being *used directly* by the organism or of being built up into the characteristic substances of the body.

Absorption of Carbohydrates.—We have seen in considering the various digestive juices that all the carbohydrates are hydrolysed to monosaccharides in the intestinal tract. For convenience these reactions may be summarised:—



When, however, the blood is examined it is found that *glucose* only is present normally, since fructose and galactose are converted into glucose by the liver. This is, indeed, made the basis of the fructose (lævulose) test for liver efficiency. A normal man is considered to be able to transform 100 grams of fructose without any appearing in the urine. It is interesting to observe that considerable differences exist in the ease with which the different monosaccharides are absorbed, thus showing a selective action on the part of the intestine.

For example, glucose is more easily absorbed than lactose or xylose, although the latter has a smaller molecule. This is in direct conflict with physical laws and can only be explained as a result of vital action on the part of the cells.

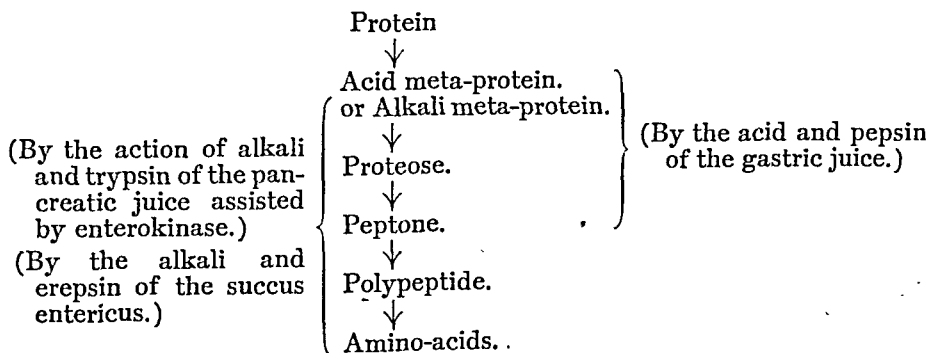
The low sugars are absorbed from any concentration with a velocity which represents the greatest possible permeability of the mucosal membrane for molecules of this size. For sugars which are not selectively absorbed, such quantities could only diffuse from extremely high concentrations (Verzár).

According to Verzár this activity process is connected with a phosphorylation* of sugars, which occurs after their diffusion into the mucosal cells. Through the constant transformation of the diffused substances the diffusion gradient is kept high, and this synthesis finally acts by increasing the diffusion process, and hence the velocity of absorption.

It has been found that this process of phosphorylation, and with it the selectivity of sugar absorption, can be inhibited by moniodo-acetic acid and other substances (through influencing certain cell processes which finally lead to phosphorylation). The extirpation of the adrenals also inhibits the selective absorption of glucose (Verzár).

If any disaccharide such as lactose is injected into the blood, it is excreted by the kidney as a foreign substance.

Absorption of Protein.—We have seen in relation to digestion that the proteins of the diet are hydrolysed to amino-acids by various enzymes. The steps may conveniently be summarised thus:—



The final stage may actually take place within the epithelial cells of the intestine itself. It is also interesting to observe that, although physiologically protein is fully digested before absorption, in certain circumstances it need not all be so hydrolysed before it is absorbed. Even in the absence of enzymes, the animal's own

* The term "phosphorylation" is given to the formation of phosphorus-containing compounds. (See Chemical Changes in Muscle.)

serum placed in the intestine is absorbed, and to a lesser extent foreign proteins may be absorbed. This fact is of considerable importance in practical medicine, since healthy normal persons who are hypersensitive to certain proteins (such as those of eggs, lobster, or strawberries) may react violently and develop an attack of asthma or a severe rash if they take quite minute quantities of the protein to which they are hypersensitive. This indicates that some absorption may take place before digestion is complete. How exactly this happens is unknown.

The normal course of events is that the main bulk of the food proteins are broken up into their constituent amino-acids, and it is in this form that they are absorbed. If an animal receives, instead of protein, the final cleavage products of pancreatic digestion, it continues to maintain its nitrogenous equilibrium; that is to say, the cells of the body are able to synthesise tissue-proteins from the fragments of the food proteins.

It is somewhat difficult to find the amino-acids in the blood during absorption, for several reasons: (1) the absorption during any given time is slow, and the products are diluted with the whole volume of the blood; (2) the presence of coagulable proteins in the blood in large quantity renders a search for the amino-acids difficult; and (3) when the amino-acids get into the blood they do not accumulate there, but are rapidly removed by the cells of the tissues, especially of the liver and muscles. In spite of these difficulties, Leathes, Howell, and, later, Folin and others succeeded in demonstrating that during absorption the non-protein (that is, the amino-acid) nitrogen of the blood increases and, if known amounts of protein is administered it is found that the amino-nitrogen corresponds to the amount absorbed (Kúthy).

There is now definite evidence that the amino-acids are absorbed as such into the blood-stream, since they can be dialysed out of the blood by passing the blood through tubes composed of semi-permeable collodion membrane surrounded by saline solution. The diffusible substances, such as sugar and amino-acids, pass through the membrane into the saline and can be estimated. This may be shown by the Abel's *vivi-diffusion* apparatus. This consists of several such tubes in parallel, inserted between the two cut ends of an artery (clotting being prevented by an anti-coagulant, such as leech extract). By this means it has been found that the amino-acids such as alanine and histidine may be recognised and it has been demonstrated that the amino-acid content of the blood increases after a protein meal. It is of interest that many of the individual amino-acids are almost insoluble, but they increase the solubility of each other very markedly by the process of *hydrotrophy* (see below). Polypeptides are, however, also absorbed (Loudon).

Absorption of Fats.—If an animal is given a fatty meal, killed, and sections of the intestine stained with osmic acid, it is seen (fig. 160) that the columnar epithelial cells become first filled with fatty globules of varying size, which are generally larger near the free border. They are then transferred to the amoeboid cells of the lymphoid tissue beneath: these ultimately penetrate into the central *lacteal*, where they either disintegrate or discharge their cargo into the lymph stream. The globules are by this time divided into very minute ones, the particulate basis of *chyle* and under the microscope these chylomicrons can be counted (Frazer).

The chylomicrons are about one-fortieth of the size of the globules of milk, and likewise cause the chyle to appear white, and are composed of neutral fat. They are at a maximum about two hours after a meal.

The great difficulty in fat absorption is to explain how the fat first gets into the columnar epithelium.

A central observation has been the work of Munk and, later, of Moore and Rockwood, who showed that in the intestine fat may be broken down into glycerol and fatty acids, in which form or as soaps they may be absorbed; preliminary emulsification is advantageous for the formation of these substances, but is not essential.

According to Mellanby the emulsified fat can pass freely into the columnar cells of the villi without previous hydrolysis, for it has been observed that neutral fat emulsified with bile can be absorbed from the duodenum into the lacteals of animals in which both the pancreatic and bile ducts have been ligatured. Moreover, Frazer and Stewart have been able to stain neutral fats in the fat depôts of the body after the administration of stained neutral fats but not after fatty acid and glycerol, while the addition of lipase

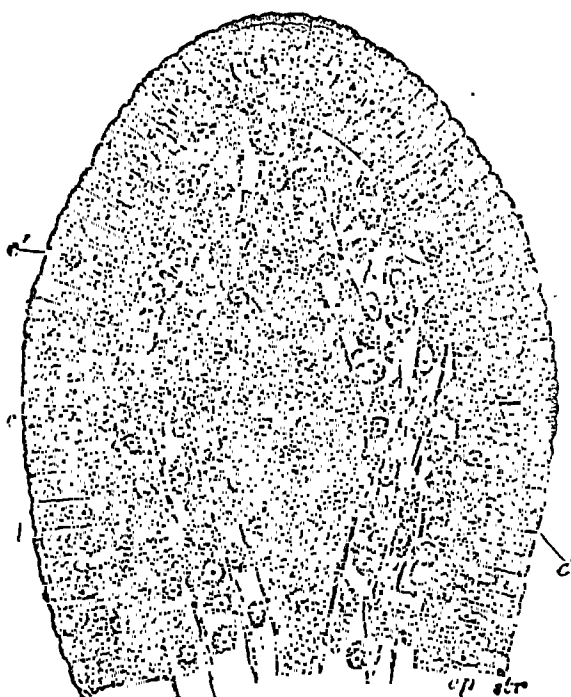


FIG. 160.—Section of the villus of a rat killed during fat absorption. *ep*, Epithelium; *str*, striated border; *c*, lymph-cells; *c'*, lymph-cells in the epithelium; *l*, central lacteal containing disintegrating lymph corpuscles. (E. S. Schafer.)

to human diet reduces the amount of fat in the blood. The main function of the lipase is considered to be the production of a small amount of hydrolysis of the fat, so that a small amount of soap is formed. This soap still further facilitates emulsification, but it is doubtful if soaps play much part in absorption as such, since when the intestine is acid as is usual (except for a short length below the entrance of the pancreatic duct) they cannot exist.

It has now been shown that even paraffin may be absorbed if it is adequately emulsified and put into the duodenum (Mellanby, Frazer), but this does not normally occur, as adequate emulsification does not take place. In this connection it should be noted that soap is about a twelve times better emulsifying agent than bile.

According to Verzář the fatty acids combine with the paired bile acids to form compounds, which are not only water-soluble and diffusible, but also especially stable at the slightly acid reaction of the intestine. This process is known as hydrotropy (see below). This bile-fat complex is broken down again in the mucosal cell. The bile acids are adsorbed on to mucosal epithelium, so that they are able to dissolve a much greater quantity of fatty acids than *in vitro*.

The fatty acid which is now in the cell combines with the glycerol, which is absorbed at the same time, to resynthesise neutral fat. This synthesis passes through an intermediate stage of phosphatide formation. The glycerol is phosphorylated and combines with the fatty acids. Thus the diffusion gradient into the cells for the fatty acids is increased. The synthesis of neutral fat, *via* the formation of phosphatide, is therefore an accelerating factor in the absorption of fat, just as the phosphorylation of glucose accelerates the absorption of this sugar. Also this synthesis may produce the specific fats of the body and render the fatty acids non-toxic.

In the mucosal epithelium the phosphatide is transformed again into neutral fat and (for the most part) appears as such in the lymph. Significant but varying amounts escape this transformation, and appear in the lymph as phosphatide (lecithin), and so increase the lecithin content of the blood during fat absorption. There seems to be no difficulty in explaining how the fat leaves the blood-stream again, since the capillary walls have a permeability comparable with artificial membranes through which a great part of the serum-fat can diffuse out (Verzář).

The intermediate synthesis of the fatty acids to phospholipoids can be inhibited by monoiodoacetic acid and by phloridzin, drugs which inhibit phosphorylation processes. Fat is then not absorbed, except for a slow diffusion of fatty acids through the intestine.

In the same way the extirpation of the adrenals inhibits neutral fat absorption, and the administration of adrenal cortex hormone (eucortone) restores the normal rate of absorption. This would appear to be due to the lack of alkali which occurs from the sodium loss through the kidneys. The absorption of fatty acid is not affected (Frazer).

The different views of Mellanby and Verzář are not mutually exclusive as at first sight appears. There seems to be little doubt that the exact method of absorption of fat varies in different animals according to their habit of diet. It may be that the cells of the villi can exercise some selective action.

It seems most likely that both bile and lipase play an important part in fat absorption in man, for excess of fat in the faeces is found both in pancreatic disease and in biliary obstruction.

It has long been known that, if fat is given to an animal, only 60 per cent. can be recovered from the thoracic duct into which all the lacteals pour their chyle. The work of Frazer and Stewart now indicates that such fat as is digested passes into the portal blood-stream and thus the remaining 40 per cent. is accounted for. They suggest this partition may determine the subsequent utilisation and deposition respectively of the fat. (See Frazer, 1940.)

It has been suggested from observations on the tail of the tadpole that the leucocytes, which we know are very active during digestion, are concerned in fat transport since they have been seen loading and unloading.

In the case of sterols there is also a selective absorption of cholesterol in comparison with other sterols. The process is also an esterification (Verzář).

Since *alcohol* is extremely soluble in lipoids as well as in water, there is every likelihood of its rapid absorption. Experience shows that a concentrated alcoholic solution is absorbed especially quickly from an otherwise empty stomach, and acts on the central nervous system in a few minutes, but food causes delay.

The Nature of Absorption.

The intestinal mucosa can be shown to act as a semi-permeable membrane. Thus, if water is placed in a loop of intestine tied off with its blood supply intact, the water is absorbed into the blood. If, however, a strong salt solution is placed in the loop, water is withdrawn from the blood into the loop.

Osmosis and diffusion may then be held to explain the absorption of water and of solutions of a lower osmotic pressure than the blood. It seems likely that diffusion is responsible for the absorption of solutions of higher osmotic pressure, for we know that even 1.5 NaCl is absorbed. In this the enormous area of the

intestine assists and it is most probable that a further hastening of the process may occur as a result of a pumping action of the villi which may suck into themselves during their relaxation. The exact function of this *pumping action of the villi* is unknown, but the fact that it takes place in that part of the intestine where absorption is greatest, that it occurs only during digestion, and that the movements are influenced like those of the gut generally suggest that they are intimately connected with absorption, which must certainly be hastened by such activity (Verzár).

How far filtration other than that caused by the villi is concerned is difficult to decide, but there seems good reason to believe that the contractions of the large intestine bring about a high hydrostatic pressure. No such rise in pressure has been demonstrated in the small intestine.

A number of physical processes influence absorption less directly. Amongst these is surface activity and emulsification or hydro-tropy by which insoluble substances such as fats become very finely subdivided and diffusible as a result of a greatly reduced surface tension from the action of bile salts. Electric phenomena, ionic distribution, acidity, and changes in the colloidal state of the cells of the mucosa and of the food also have a considerable influence.

A number of the phenomena concerned in absorption can, however, only be explained as being due to the vital activity of the cells themselves. Thus it is found that 0.4 per cent. sodium chloride is more rapidly absorbed than water, while isotonic solutions of sodium or magnesium sulphate are unabsorbed. There is also, as we have seen (p. 439), considerable selectivity in regard to the different carbohydrates, while most difficult to understand is the fact that if some of the animal's own serum is placed on the gut it is absorbed. Such facts can only be explained as a vital action of cells of the mucous membrane, upon which must also depend nervous and drug action. The necessity in absorption for the presence of calcium as shown by Macgee, and of oxygen even for the absorption of saline (Brodie) is also suggestive of the importance of vital activity. This is still further supported by the influence of vitamin D which is necessary for calcium absorption. It has been shown that if the mucosa is removed by fluoride, absorption ceases altogether, but since this does not always occur when the mucosa is otherwise removed the cessation may be attributed to damage to the surface of the gut. It can, however, be said that there are many points in relation to absorption in regard to which we have no knowledge. The great difficulty in the study of the problem is the maintenance of the intestinal wall under controlled conditions without interfering with its vitality.

Hydrotrophy.—Although substances may be insoluble in water they may be rendered soluble by the presence of another substance in solution. We have already remarked on the effect of the individual amino-acids on their solubility and of bile salts on fatty acids. This so-called process of hydrotrophy is well known in industrial chemical processes; for example, calcium carbonate is soluble in a solution of sodium salicylate, and barium sulphate is soluble in sulphuric acid. Hydrotrophy may also be important in the absorption of calcium. It would seem that the presence of one substance in solution affects the molecular structure of water itself upon which solution depends.

REFERENCES.—Goldschmidt, 1921; Magee, 1930; Verzáar and Macdougall, 1936.

THE FUNCTIONS OF THE LARGE INTESTINE.

These are mechanical, absorptive and excretory.

The *mechanical functions* of the large intestine comprise the storage of fæces and their evacuation at due intervals.

The large intestine *absorbs* chiefly water. On the average about 500 c.c. of fluid contents pass the ileo-cæcal valve *per diem*; from this the nutritious substances have been for the most part absorbed by the small intestine. From this 500 c.c. the large intestine absorbs about 400 c.c. of water, leaving 100 c.c. in fæces; these figures are susceptible of considerable variation, notably in the pathological states of which diarrhoea is a symptom, but it is to be noted that the normal slow passage of the contents through the colon permits of considerable inspissation. If for any reason stagnation occurs, *e.g.* if the call to defæcation is neglected, the fæces become dry and hard. This is a common cause of chronic constipation. In addition to water the large intestine can absorb salts, glucose and perhaps amino-acids. Thus saline fluid is slowly absorbed, and rectal administration of saline is a valuable means of treatment of post-operative shock in which condition there is a reduction of circulating blood volume. Since, however, the mucous membrane of the large intestine produces no digestive enzymes, proteins introduced into the rectum are not absorbed, since they are not digested. "Nutrient" enemata, therefore, are of little value to the patient who cannot take food by the normal channel; they serve merely to nourish the bacteria which abound in the colon. Even the absorption of glucose is so slow that it does not raise the blood sugar.

Various drugs are absorbed when injected into the rectum in dilute solution; a state of general anæsthesia can be induced in this way. This is the usual way in which the basal anæsthetic avertin (tribromethyl alcohol) is administered.

The *excretory activities* of the large intestine cover a considerable range of substances, some physiological, the majority pharmacological. Normally iron, as sulphide, and calcium and magnesium as phosphates, leave the body by this route. The ratio of the amount of calcium and magnesium excreted by the bowel to that removed by the kidney depends on the quantity of acid radicals excreted by the latter. If acids are administered, more calcium and magnesium leave by the urine as soluble salts, whereas if there are fewer acid radicals in the food the amount of calcium and magnesium passing out as insoluble phosphates in the *fæces* is increased.

In brief, the large intestine may be regarded as the principal channel for the excretion of insoluble substances which could not easily be passed out by the kidneys.

In many herbivora, viz. those in which the stomach is not complex, *e.g.* the rabbit, bacterial activity occurring in the *cæcum* is important in dissolving the cellulose of the walls of the vegetable cells which constitute their diet. Some of the products of the decomposition of cellulose and the liberated cell contents are then available for absorption. On the other hand, it has been possible to rear suitable animals on quite sterile food (after separation from the mother by *Cæsarean* section), and the *fæces* of animals living in the Arctic regions is said to be free from bacteria.

Normally the upper part of the intestine is sterilised by the action of the acid of the stomach. It is only when this acid is deficient, or the bacteria very excessive in the food or water, that the small intestine becomes infected. The fact that fluids leave the stomach rapidly accounts for the fact that milk and water are such admirable carriers of intestinal infection such as typhoid fever.

To what extent the bacterial content of the large intestine is of economic value in man is difficult to determine. Some clinicians hold that an excess of bacteria in the *fæces* is definitely harmful, and certainly we have good reason to believe that this is so, especially if they occur in the small intestine where absorption of their products may occur. At the same time the body is definitely protected from the invasion of bacteria from the large intestine. Barclay-Smith has emphasised the importance of the Peyer's patches in the lower end of the ileum in protecting against bacterial spread upwards from the large intestine. The solitary follicles, also composed of lymphoid tissue, appear to play a similar important part in the large intestine, as is seen by the fact that they take up pathological bacteria in disease, *e.g.* dysentery.

The Chemistry of Bacterial Action.

If an artificial pancreatic digest is kept at ordinary room temperature the fluid very soon becomes putrid, unless special

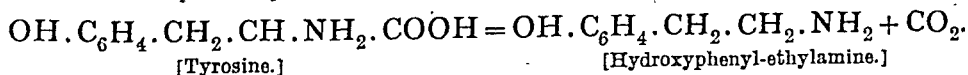
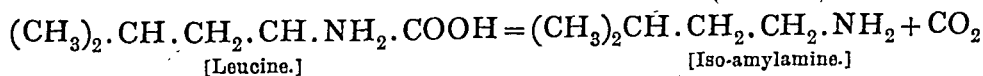
precautions to exclude or kill bacteria are taken. It is often difficult to say where pancreatic action ends and bacterial action begins, as many of the bacteria that grow in the intestinal contents produce enzymes which act in the same way as the pancreatic juice. Some form sugar from starch, others peptones and amino-acids from proteins, while others, again, break up fats. There are, however, certain actions that are entirely due to these putrefactive organisms.

i. On carbohydrates. The most frequent fermentation set up is the lactic acid fermentation: this may go further and result in the formation of carbonic acid, hydrogen, and butyric acid. Cellulose is broken up into carbonic acid and methane. This is one of the chief causes of the gases in the intestine, the amount of which is increased by coarse vegetable food. The vegetable food probably acts by reducing the acidity of the saliva and, because it is liable to be insufficiently broken down, the starch in it escapes digestion. It has been shown by Knott that the HCl of the stomach normally assists this breakdown and that its absence is liable to increase fermentation. Sometimes the volume of carbohydrate taken, *e.g.* potatoes, is in excess of what can be digested by the various diastases. Flatulence in man is commonly caused by such fermentation, but more commonly by air-swallowing with fluids.

ii. On fats. In addition to acting like lipase, bacteria produce lower acids (valeric, butyric, etc.). The formation of acid products from fats and carbohydrates gives to the intestinal contents an acid reaction. Research shows that the contents of the intestine become acid much higher up than was formerly supposed. These organic acids do not, however, hinder pancreatic digestion.

iii. On proteins. Peptones, amino-acids, and ammonia are produced; but the enzymes of these putrefactive organisms have a specially powerful action in liberating substances having an evil odour, such as skatole (C_9H_9N). Skatole originates from the indole radical of tryptophan, one of the amino-acids of protein.

iv. On amino-acids. The most frequent change consists in the splitting off of carbonic acid from their $COOH$ group, and the production of amines, as shown in the following examples:—



Such basic products if absorbed and not excreted by the kidney may produce harmful effects. Both the above produce a high blood-pressure. Their amount may be lessened by diminishing the protein intake in the food. Another amine called histamine is similarly

produced by a loss of CO_2 from the amino-acid histidine. This causes a dilatation of capillaries (*q.v.*) (Dale and Richards) which is associated with compensatory arterial constriction (McDowall). Whether this constriction is in some way responsible for the high blood-pressure which is associated with excessive meat eating is a matter of debate, but it may readily be that the compensatory constriction leads to hypertrophy and eventually to permanently increased peripheral resistance.

Ammonia-producing organisms flourish best in the lower regions of the small intestine; the ammonia neutralises the organic acids produced higher up. In the large intestine the contents may have an alkaline reaction.

Sour milk has in past years been extolled not only as a useful food, but as a cure for many dyspeptic disorders. Although its efficacy in this direction has been much exaggerated, its usefulness in certain cases is explicable on the ground that the lactic acid bacillus, which is a harmless one in itself, possesses the power, when it is actively growing, of destroying other micro-organisms of a harmful kind.

The *fæces* on an ordinary mixed diet contain comparatively little food residues, and a small quantity is excreted even during starvation. Voit and Hermann showed independently that an intestinal loop which had been emptied and separated from the rest of the bowel contained, a few days later, material identical with *fæces*, and consisting of intestinal juice, desquamated epithelial cells, and bacteria. The increase in the amount of *fæces* which occurs when food is taken, even when the food is free from cellulose, is due to the mechanical and chemical stimulation which leads to an increase in the *succus entericus*, and in the shedding of epithelial cells. Addition of protein to the diet makes practically no difference to the nitrogen in the *fæces* under normal conditions.

The addition of cellulose to the diet increases the bulk of the *fæces*, partly because much of the cellulose is excreted unchanged, partly because it stimulates the mucous membrane to secrete more *succus entericus*, and finally because the larger food residue favours the development of bacteria. On an average, from one-fifth to one-third (varying with the diet) of the weight of dried *fæces* consists of bacteria. Strasburger estimated that about 128,000,000,000,000 bacteria are evacuated in the *fæces* of a man every day. The vast majority of these are dead.

When cellulose is absent from the diet, the *fæces* contain from 65 to 75 per cent. of water.

The ash contains mainly calcium phosphate, with small amounts of iron and magnesium. The ethereal extract contains cholesterol, lecithin, fatty acids, soaps, and a very small amount of neutral fat. The presence of excess of neutral fat

indicates deficient pancreatic secretion, while excess split fat, *i.e.* fatty acids and soaps, is found in jaundice. The proteins are chiefly mucin and nucleo-protein, and are derived not from the food but from the intestinal wall, or are contained in the bacteria; no doubt a large part of the ethereal extract is also supplied by the bacteria.

Cellulose is thus the only important constituent of the food which is unaffected by the digestive juices, although a variable amount, which is largest in herbivorous animals, undergoes bacterial decomposition. The presence of cellulose also interferes with the absorption of proteins, for the digestive juices have difficulty in penetrating the cellulose membranes of vegetable cells. Thus Voit found that 42 per cent. of the nitrogen in the food was lost in the faeces of a vegetarian. This is due solely to the cellulose and not to any difference in the digestibility of animal and vegetable proteins, for if vegetable food is finely subdivided, and then thoroughly cooked and softened, this loss is lessened, and if vegetable protein is entirely freed from cellulose, it is as thoroughly absorbed as animal protein. 15 per cent. of the dry substance of green vegetables and brown bread, 20 per cent. of carrots and turnips, and a still larger proportion of beans are lost in the faecal residue.

The intestinal contents travel more rapidly when vegetables are present, for the indigestible cellulose stimulates peristalsis, and therefore a large quantity of water escapes absorption in the colon. Thus on an ordinary mixed diet 35 grams of dry substance and 100 grams of water are daily excreted in the faeces, whereas on a vegetable diet the quantities are 75 and 260 grams respectively.

The fat in the faeces is of some considerable importance as an excess—provided, of course, that the consumption of fat has not been excessive—indicates a faulty digestion or absorption of fats. This may result from lack of bile or pancreatic juice. It must be understood that a certain small amount is normal even on a fat-free diet or during starvation. When fat absorption is deficient there may be an excess of “split fat,” *i.e.* fatty acids in the faeces. Otherwise the fat of the faeces is chiefly neutral and is accompanied by sterols and phospholipides.

The colour of the faeces is important clinically. They tend to be pale on a diet containing no red meat and when there is excessive fat. A dark colour is produced by meat and by an excessive amount of bile such as occurs after magnesium sulphate. Sulphides are also dark. Black stools due to iron occur in hæmorrhage especially from the upper part of the alimentary canal. Blood from the rectum or commonly from bleeding piles or a fissure at the anus is, however, bright red.

The reaction of the faeces varies from pH 7 at the surface to as low as 4.8 at the centre of the mass.

CHAPTER XXXIII

THE MECHANICAL PROCESSES OF DIGESTION

UNDER this head we shall study the neuro-muscular mechanism of the alimentary canal, which has for its object the onward movement of the food, and its thorough admixture with the digestive juices. We shall therefore have to consider mastication, deglutition, the movements of the stomach and intestines, defæcation, and vomiting.

THE TEETH.

During the course of his life, man, in common with most other mammals, is provided with two sets of teeth; the first set, called the *temporary* or *milk-teeth*, makes its appearance in infancy, and is in the course of a few years shed and replaced by the second or *permanent* set.

The deciduous or milk-teeth are ten in number in each jaw, namely, on either side from the middle line two *incisors*, one *canine*, and two deciduous *molars*, and are replaced by ten permanent teeth. The number of permanent teeth in each jaw is, however, increased to sixteen by the development of three molars on each side of the jaw, which are called the permanent or true molars.

Structure of a Tooth.

A tooth is generally described as possessing a *crown*, *neck*, and *root*.

The *crown* is the portion which projects beyond the level of the gum. The *neck* is that constricted portion just below the crown which is embraced by the free edges of the gum; and the *root* includes all below this.

A tooth is found to be composed of a hard material, *dentine* or ivory, which is moulded around a central pulp cavity (fig. 161).

The *tooth-pulp* is composed of loose connective tissue, blood-vessels, nerves, and large numbers of cells of varying shapes; on the surface in close connection with the dentine is a specialised layer of cells called *odontoblasts*, which are elongated columnar cells each with a large nucleus at the tapering end farthest from the *dentine*.

The dentine resembles bone in chemical composition, but has only 10 per cent. of water. It contains a vast number of minute tubes which connect with the pulp and which contain the exquisitely sensitive nerve fibrils from a layer of stellate nerve-cells beneath the odontoblasts (Mummery).

The blood-vessels and nerves enter the pulp through a small opening at the apical extremity of each root. The nerves terminate by branching into fine fibrillæ which enter the tubes of the dentine.

A layer of very hard calcareous matter, the **enamel**, caps that part of the dentine which projects beyond the level of the gum.

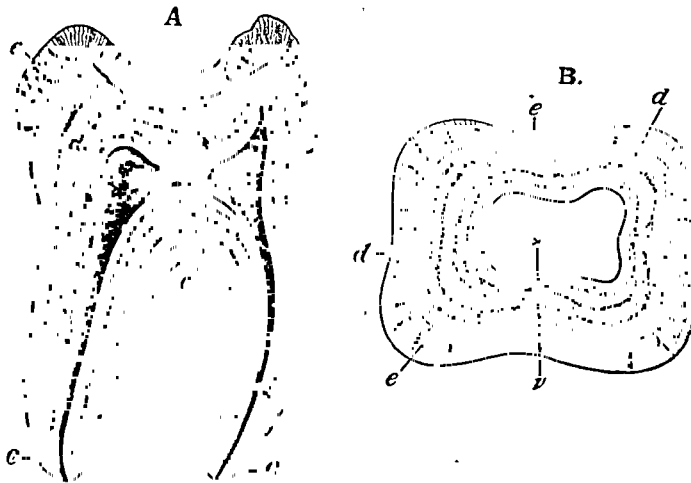


FIG. 161.—A, Longitudinal section of a human molar tooth; c, cement; d, dentine; e, enamel; v, pulp-cavity. (Owen.)
B, Transverse section. The letters indicate the same as in A.

Sheathing the portion of dentine which is beneath the level of the gum is a layer of true bone, called the *cement* or *crusta petrosa*.

Enamel is the hardest tissue in the body, and contains a minimum amount of organic material and less than 3 per cent. of water. It is made up of minute prisms of the same salts as those of bone, which are set on end and which fit on to the surface of the dentine. Some of the larger spaces between the prisms communicate with the dental tubules and it has been suggested that fluids may pass between the prisms.

MASTICATION.

The act of mastication is performed by the biting and grinding movement of the lower range of teeth against the upper. The simultaneous movements of the tongue and cheeks assist partly by crushing the softer portions of the food against the hard palate and gums, and thus supplement the action of the teeth, and partly by returning the morsels of food to the teeth again and again, as they are squeezed out from between them, until they have been sufficiently chewed.

The act of mastication is much assisted by the saliva.

Mastication is much more thoroughly performed by some animals

than by others. Thus, dogs hardly chew their food at all, but the œsophagus is protected from abrasion by a thick coating of very viscid saliva which lubricates the pieces of rough food.

In vegetable feeders, on the other hand, insalivation is a much more important process. This is especially so in the ruminants; in these animals, the grass, etc., taken, is hurriedly swallowed, and passes into the first compartment of their four-chambered stomach. Later on, it is returned to the mouth in small instalments for thorough mastication and insalivation; this is the act of *rumination*, or "chewing the cud"; the food is then once more swallowed, and passes on to the digestive regions of the stomach.

In man, mastication is also an important process, and in people who have lost their teeth severe dyspepsia is sometimes produced, which can be cured by the use of artificial teeth.

DEGLUTITION.

When properly masticated, the food is transmitted in successive portions to the stomach by the act of deglutition or swallowing. This, for the purpose of description, may be divided into *three* acts. In the first, particles of food collected as a bolus are made to glide between the surface of the tongue and the palatine arch, till they have passed the anterior arch of the fauces; in the second, the bolus is carried through the pharynx; and in the third, it reaches the stomach through the œsophagus. These three acts follow each other rapidly. (1) The first act is *voluntary*, although it is usually performed unconsciously; the morsel of food when sufficiently masticated is pressed between the tongue and palate, by the agency of the muscles of the former, in such a manner as to force it back to the entrance of the pharynx. (2) The second act is the most complicated, because the food must go past the posterior orifice of the nose and the upper opening of the larynx without entering them. When it has been brought, by the first act, between the anterior arches of the palate, it is moved onwards by the movement of the tongue backwards, and by the muscles of the anterior arches contracting on it and then behind it. The root of the tongue being retracted, the larynx is raised with the pharynx and carried forwards under the base of the tongue; the closure of the glottis is secured by the contraction of its own muscles: so that there is little danger of food passing into the larynx so long as its muscles can act freely. At the same time, the raising of the soft palate, so that its posterior edge touches the back wall of the pharynx, and the approximation of the sides of the posterior palatine arch, which move quickly inwards like side curtains, close the passage into the upper part of the pharynx and the posterior nares, and form an inclined plane,

along the under surface of which the food descends; then the pharynx, raised up to receive it, in its turn contracts, and by the successive action of its three constrictors, the food is forced onwards into the cesophagus. These reactions take place *reflexly* from the stimulation by the food in the pharynx. This is shown by the fact that the reflex may be abolished by spraying the back of the throat with a local anæsthetic. (3) In the third act, in which the food passes through the cesophagus, every part of that tube, as it receives the morsel and is dilated by it, is stimulated to contract: hence an undulatory or *peristaltic contraction* of the cesophagus occurs. If we suppose the bolus to be at one particular place in the tube, it acts stimulatingly on the circular muscle-fibres behind it, and inhibitingly on those in front; the contraction therefore squeezes it into the dilated portion of the tube in front, where the same process is repeated, and thus travels along the whole length of the tube. The second and third parts of the act of deglutition are involuntary. The action of these parts is more rapid than peristalsis usually is. This is due to the large amount of striated muscular tissue present. It serves the useful purpose of getting the bolus as quickly as possible past the opening of the respiratory tract.

The swallowing of both solids and liquids is a muscular act, and can, therefore, take place in opposition to the force of gravity. Thus, horses and many other animals habitually drink against gravity, and the same feat can be performed by man.*

In swallowing liquids in the ordinary way, however, the mechanism is a different one; the two mylo-hyoid muscles form a diaphragm below the anterior part of the mouth. The stylo-glossi draw the tongue backwards and elevate its base; the two hyo-glossi act with these, pulling the tongue backwards and downwards. The action of these muscles resembles that of a force-pump projecting the mass of fluid down into the cesophagus; it reaches the cardiac orifice with great speed, and the pharyngeal and cesophageal muscles do not contract on it at all, but are inhibited during the passage of the fluid through them. (Kronecker.)

This is proved in a striking way in cases of poisoning by corrosive substances, such as oil of vitriol; the mouth and tongue are scarred and burnt, but the pharynx and cesophagus escape serious injury, so rapidly does the fluid pass along them; the cardiac orifice of the stomach is the next place to show the effects of the corrosive. Kronecker's view has also been confirmed in man by the X-ray method.

* The fluid is, however, liable to pass into the nose unless swallowing movements are continued after the mouth is empty.

Nervous Mechanism.—The nerves engaged in the reflex act of deglutition are:—

Sensory: branches of the trigeminal nerve supplying the soft palate and tongue; glosso-pharyngeal, supplying the tongue and pharynx; the superior laryngeal branch of the vagus, supplying the epiglottis and the glottis. The *motor* fibres concerned are: branches of the trigeminal, supplying part of the digastric and mylo-hyoid muscles, and the muscles of mastication; the bulbar part of the accessory through the pharyngeal plexus, supplying the levator palati, probably by rootlets which are glosso-pharyngeal in origin; the glosso-pharyngeal and vagus, and possibly the bulbar part of the accessory, supplying the muscles of the pharynx through the pharyngeal plexus; the vagus, in virtue of its accessory roots, supplying the muscles of the larynx through the inferior laryngeal branch; and the hypo-glossal, the muscles of the tongue. The nerve-centres by which the muscles are harmonised in their action are situated in the medulla oblongata.

Stimulation of the vagi gives rise to peristalsis of the œsophagus. The cell-stations of these fibres are in the ganglion trunci vagi. Division of both vagus nerves produces paralysis of the œsophagus and stomach.

In discussing peristalsis on a previous occasion, we have already stated that it is a rhythmic movement of smooth muscle rather than of nerve; though normally it is controlled and influenced by nervous agency. This nervous control is especially marked in the œsophagus, for if that tube is divided across, leaving the nerve branches intact, a wave of contraction will travel from one end to the other across the cut.

Peristalsis.—This is the movement by which the contents of many tubes throughout the body are moved on. It consists essentially of a progressive wave of contraction which is preceded by a wave of relaxation. This may readily be observed if the abdomen of an anæsthetised animal is opened under warm saline. The movements continue if a piece of the gut is kept in a bath of oxygenated warm Ringer's solution. They are set going if a suitable object is placed in the lumen of the gut to stretch its wall. The normal stimulus to such movements, therefore, we may consider to be the material within the intestine. In the lower end of the gut the undigested cellulose of the food must become the chief stimulus; hence the importance of eating fruit and vegetables which add to the undigestible bulk of the food. We have already noted that the best stimulus to smooth muscle is stretching. As Starling showed, however, a mere pinch of the intestine will cause a typical peristaltic wave to pass downwards. The initial wave of relaxation may be shown by placing in the lumen a small balloon attached to a

tambour. Normally, the peristaltic waves are co-ordinated like those we have referred to in the oesophagus. The co-ordination is considered to be effected through Auerbach's plexus of nerves, which lies between the two muscle coats. Yanasi found that the intestinal muscle of the embryo guinea-pig will contract when directly stimulated but will not do so spontaneously until the plexus of Auerbach has been developed.

Peristalsis may be influenced chemically. Drugs given for the relief of diarrhoea or constipation act in various ways; some affect the amount of secretion, and thus increase or decrease the fluidity of the intestinal contents; others act on the muscular tissue or its nerves and so influence the amount of peristalsis. Organic acids, including the amino-acids, produced during digestion, will increase peristalsis. The bile has a similar action, but only on the large intestine; various oils act in the same way; certain gases also, but here again the mechanical effect of distension is a factor to be reckoned with. A vegetable diet stimulates peristalsis, partly for mechanical reasons—the presence of indigestible cellulose and formation of gas—partly for a chemical reason, namely, the production of organic acids.

The rhythmical power of the intestine is best developed in the upper part where the contractions are much more rapid than in the lower. In the lower parts, however, the contractions are greater. According to Alvarez these differences depend on differences in the metabolism of the muscle of the different parts.

MOVEMENTS OF THE STOMACH.

The gastric fluid is assisted in accomplishing its share in digestion by the movements of the stomach. The movements of the stomach have been studied by three main methods. We may study the behaviour of isolated strips or we may pass down the oesophagus balloons connected to tambours which register changes in pressure. By far the most important results have, however, resulted by the X-ray method introduced by Cannon. The individual or animal swallows food mixed with bismuth subnitrate or an insoluble barium salt which renders the gastric contents opaque to the rays.

It is now recognised that the shape of the stomach may vary appreciably in different individuals, and so also may the movements. There are two extremes: (1) The J-shaped stomach which hangs down, so that when the subject is standing the lower curvature hangs down below the interiliac line, and (2) the so-called steer-horn stomach which is more horizontal and hangs higher in the abdomen. The J-shaped stomach is the more common.

In practice it has not been easy to study the movements of the

stomach as X-rays can only be applied for very short periods because of the danger of burning the skin.

The method was originally applied to man by Hurst of Guy's Hospital, who observed that the fundus and body of the stomach are relatively inactive and adapt themselves to the size of the contents; they display what may be described as postural tone. Small peristaltic waves are seen to commence high up in the body, and when they reach the incisura angularis they become more marked till in the pyloric region they are so active that the term pyloric mill has been applied to this region (the pyloric antrum). The waves are commonly at intervals of 20 seconds and are often in groups. By putting bismuth pellets into the stomach it has been observed that

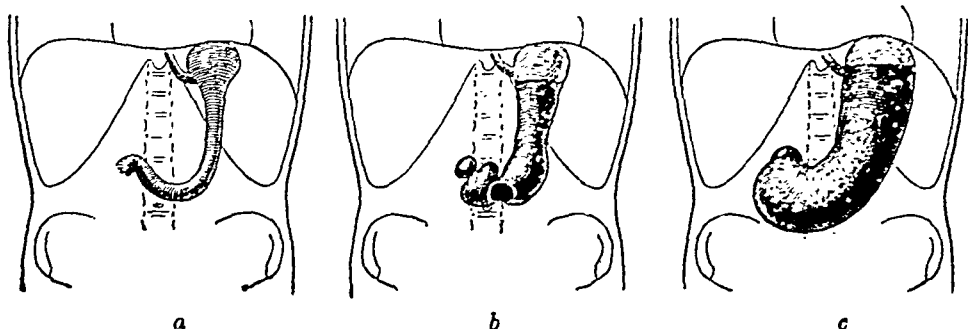


FIG. 162.—(a) View of the empty stomach in vertical position; (b) stomach as seen soon after a bismuth meal; note the constriction due to peristaltic waves at the pyloric end; (c) view of filled stomach in vertical position. (After Hurst.)

the waves as it were waft the food to the pylorus, *i.e.*, the food does not travel so fast as the waves.

It has been demonstrated experimentally by recording the movements of isolated strips of stomach wall in Ringer's solution that the property of rhythmic movement of the pyloric canal is a property of the stomach wall itself and not due to any central connection, and that similarly the property of tone is best developed in the fundus. Fatty hypertonic meals delay emptying (McSwiney and Spurrell).

The emptying of the stomach is of increasing interest as pain in the region of the pylorus is an increasingly common complaint of civilised communities, and some think that failure of the pylorus to open, especially when the stomach is empty, to allow of the regurgitation of the neutralising juice of the duodenum, is an important factor in the production of gastric ulcer.

The pylorus opens when the antral peristaltic waves reach it, but it may remain closed if the food is not suitable, if too acid food reaches the duodenum, if the sympathetic is very active or the pylorus unduly irritable. Waves in the duodenum corresponding

to those in the antrum take on the food. The suggestion of Cannon, that the pylorus opens when the stomach contents are acid and the duodenal contents alkaline, no longer appears to refer to the normal exit of food from the stomach, but to the reversed peristalsis which occurs when the stomach is empty. It is abundantly proven that the gastric contents, *e.g.* a glass of milk, may leave the stomach normally even when alkaline.

It should be noted that slow emptying of the stomach is probably advantageous so far as protein is concerned, as it facilitates digestion. A dog which gulps its meat digests it better than when it is given in a minced state.

The Effects of Exercise and Mental Stress.—It is on historical record that Frederick II, who ruled the Holy Roman Empire in the thirteenth century, caused two men to be given a good meal. One was allowed to rest and the other made to perform strenuous exercise. Subsequently he had them both disembowelled in his presence when it was found that in the man who had worked, the food had remained undigested in the stomach.

Other physiologists later observed that if dogs were hunted immediately after being fed the food did not leave the stomach.

Failure of the pylorus to open normally (called by Hurst achalasia) has been described as resulting from mental or physical stress, and in such circumstances the individual may experience pain (indigestion) as a result of the pyloric canal attempting to force food through the closed sphincter. The desirability of not taking a large meal before a strenuous game is then clear. It has also been shown that apparently trifling exercise or stress may delay gastric emptying, and that much benefit accrues from relaxation in pleasant company. These points are of great importance in the treatment of indigestion. What has been said in relation to the conditions which facilitate gastric secretion applies, therefore, to gastric movement also (Pembrey).

Physical movements, on the other hand, have been described as hastening the emptying.

The innervation of the stomach is discussed by McSwiney (1931).

At the upper end of the stomach is usually seen an air-pocket, which may become increased in size and press on the heart.

The tone of the stomach wall is also subject to considerable change. An instance is recorded that a student was informed that he had got into serious academic difficulty at a time when he chanced to be having an X-ray screen examination of his stomach made. At once his stomach was seen to sag until its lower border reached the pelvis. This emphasises the importance of making several X-ray examinations before a diagnosis of visceroptosis (dropped viscera) is made.

VOMITING.

The act of vomiting is preceded by a feeling of nausea, and the swallowing of a large quantity of saliva. The expulsion of the contents of the stomach, like that of mucus or other matter from the lungs in *coughing*, is preceded by an inspiration; the glottis is then closed, and immediately afterwards the abdominal muscles strongly act; but here occurs the difference in the two actions. Instead of the vocal cords yielding to the action of the abdominal muscles, they remain tightly closed. Thus the diaphragm, being unable to go up, forms an unyielding surface against which the stomach can be pressed. At the same time the *cardiac* sphincter being relaxed, and the orifice which it naturally guards being dilated, while the *pylorus* is closed, and the stomach itself also contracting, the action of the abdominal muscles expels the contents of the organ through the œsophagus, pharynx, and mouth.

It has been frequently stated that the stomach itself is quite passive during vomiting, and that the expulsion of its contents is effected solely by the pressure exerted upon it when the capacity of the abdomen is diminished by the contraction of the diaphragm, and subsequently of the abdominal muscles. The experiments and observations, however, which are supposed to confirm this statement, only show that the contraction of the abdominal muscles alone is sufficient to expel matters from an unresisting bag through the œsophagus; and that, under certain conditions, the stomach by itself cannot expel its contents. They by no means show that in ordinary vomiting the stomach is passive, and there are good reasons for believing the contrary. In some cases of violent vomiting the contents of the duodenum are passed by anti-peristalsis into the stomach, and are then vomited. Where there is obstruction to the intestine, as in strangulated hernia, the total contents of the intestine above the obstruction may be vomited.

Nervous Mechanism.—Some few persons possess the power of vomiting at will, or the power may be acquired by effort and practice. But normally the action is a reflex one.

The *afferent* nerves are principally the trigeminal, and glossopharyngeal (as in vomiting produced by tickling the fauces), and the vagus (as in vomiting produced by gastric irritants); but vomiting may occur from stimulation of other sensory nerves, *e.g.*, those from the kidney, uterus, testicle, etc. The medullary centres may also be stimulated by impressions from the cerebrum and cerebellum, producing the so-called *central* vomiting which occurs in diseases of those parts.

The *efferent* (motor) impulses are carried by the vagi to the

stomach, by the phrenics to the diaphragm, and by various other spinal nerves to the abdominal muscles.

Emetics.—Most emetics produce vomiting by irritating the stomach; some, such as apomorphine, by stimulating the medullary centres.

It was recorded by Dixon that a dog into which he had previously injected apomorphine eventually vomited when it saw the syringe, thus indicating the establishment of a conditioned reflex.

The mechanism of vomiting is discussed by Hatcher (1924).

MOVEMENTS OF THE SMALL INTESTINE.

The intestinal movements may be studied in several ways. Observations may be made on the exposed intestines when the abdomen is opened. They may be studied under more artificial conditions by taking a length of intestine from a freshly killed animal and placing it in a warm bath of oxygenated Tyrode's solution. This method is most useful for the study of the action of various drugs. The apparatus by which the movements may be recorded is described on p. 468 below, where the constitution of Tyrode's solution is also given. In man, the most valuable method is to study the movements by X-ray already referred to in regard to the stomach.

The object of these movements is to force the contents along the tube, and thoroughly to mix them with the digestive juices.

The most important movement is **peristalsis**, such as has been already described in relation to the œsophagus (p. 454). It is doubtful if intestinal peristalsis is ever so intense as that in the œsophagus, which is more under the control of the central nervous system. According to Alvarez the preceding wave of relaxation is absent and the movements consist of rapid rushes. Its rate, however, is generally slower, but varies very much—from 1 cm. per minute to 25 cm. per second. The length of the wave also varies. It may only travel a short distance or may sweep throughout the whole length of the intestine. The more rapid waves are known as the peristaltic rush and may be initiated by taking food into the stomach and especially hot fluid.

Cannon also observed, by the X-ray method in dogs and cats, **segmental movements**. They are very regular and constant. A dark shadow, due to the bismuth in the food administered, is at one moment of a certain length like a short sausage; it then constricts in the centre, and divides into two; each half divides again; then the two central segments join together, and this repeats itself every few seconds. In man, Hurst timed the rate, and found it occurred about ten times in a minute and a half. This

frequent division and subdivision not only ensures admixture with the juices, but brings every portion in turn in contact with the absorbing mucous membrane, and favours the flow of chyle and blood.

After a bismuth meal, the shadow appears in the cæcum three and a half to five hours after the food is taken. The average time is four and a half hours. The movements are greatest at the upper end of the alimentary canal where, according to Alvarez, metabolism is most active. In this region the digestive processes are most active and most juices are added to the food.

The **pendulum movements** consist of slight waves of contraction affecting both muscular coats, and these are rapidly propagated at the rate of 2 to 5 cms. per second. They cause a movement of the intestine from side to side, and occur at regular intervals of five or six seconds. They are not efficacious in moving the contents onwards, but they bring about a very thorough mixing of the contents.

The pendulum movements differ from true peristalsis in being *myogenic*; that is, they are due to the rhythmicality of the muscle-fibres themselves, and are propagated from one muscle-fibre to another. They are not abolished by cocaine or nicotine (Starling).

In addition to the movements of the intestine as a whole the **villi** exercise a pumping action. The villi contract if any mechanical stimulus is applied at their base, but it is suggested that their normal stimulus is a hormone called **villikin** which can be extracted from them and is thought to be liberated into the blood after the manner of secretin, for the placing of hydrochloric acid in the duodenum of one dog, whose blood is made to supply the intestine of another, is stated to produce movements of the villi in the latter. The muscularis mucosæ relaxes during active digestion. The muscularis mucosæ is caused to contract by adrenaline, but the exact value of the contraction of this muscle is not known.

Intestinal Gradient.—The evidence, especially that of Alvarez, is that there is a gradient of activity throughout the intestine. The upper end has a greater tone, irritability and rate of rhythmical contraction than the lower parts. Thus in studying intestinal movement pieces of the duodenum are taken for preference.

Gradient probably explains why it is impossible for an animal to survive, if a portion of intestine has its direction reversed, for the food will only pass in the one direction, *i.e.* from a region of high activity to one of a lower.

MOVEMENTS OF THE LARGE INTESTINE.

We have seen that in man the food begins to arrive in the cæcum four and a half hours after it reaches the stomach; when it arrives in the cæcum it contains 90 per cent. of water, together with

a small amount of the unabsorbed products of digestion of proteins, fats, and carbohydrates. During its passage along the large intestine these are absorbed, and most absorption appears to occur in the cæcum; the normal firm consistency of the fæces, which contain 75 per cent. of water, is not finally attained until they arrive in the pelvic colon, where they are retained until defæcation takes place.

Peristalsis in the colon occurs much more slowly than in the small intestine, and the accompanying diagram gives the time in

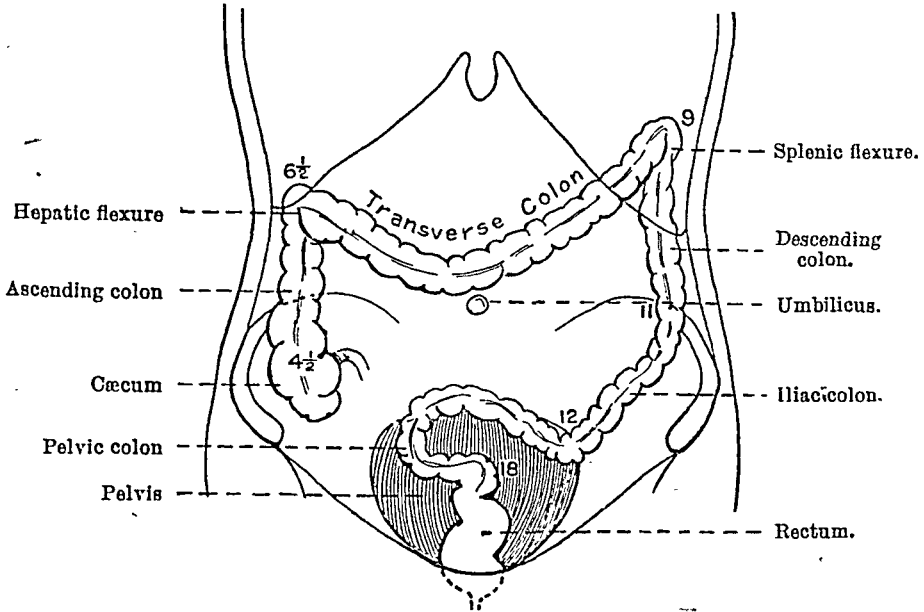


FIG. 163.—Semi-diagrammatic view of the large intestine; the figures give in hours the average times after taking a meal that its debris reaches the various parts. (Hurst.) This diagram shows the transverse colon in a higher position than it occupies when the man is erect, and rather higher than the average even in the horizontal position.

hours after the taking of a bismuth meal that the shadow appears at various points in man. It will be noted that the movement of the contents of the large intestine is slow compared with that of the small intestine; indeed, the rate may be less than a foot per hour. These observations were made in the daytime; during sleep the rate of progress may be slower. Commonly, a *mass peristalsis* occurs. It begins at the hepatic flexure and carries all before it. It may be initiated by taking food into the stomach or by emotional influences. Similar influences affect the contractions of the lower end of the ileum and normally bring about relaxation of the ileo-cæcal sphincter, *i.e.* the *gastro-ileal reflex*. The cæcum itself is remarkably inert. In the herbivora it is an important seat of the bacterial decomposition of cellulose.

Regurgitation into the small intestine is effectually prevented, partly by the ileo-cæcal valve, and mainly by a strong band of circular

muscle-fibres called the ileo-cæcal sphincter; this is normally kept in a state of tonic contraction by impulses carried by the splanchnic nerve; it is relaxed when this nerve is cut, and then the contents of the two intestines mix freely (T. R. Elliott).

Defæcation.

The rectum is a short tube about 4 or 5 inches long in man, and is normally empty until immediately before defæcation. In a person of regular habits, a glass of water on rising, and the taking of breakfast, if attended by mental quiet, combine to produce peristalsis of the colon, so that a small quantity of fæces enters the rectum, and produces the desire to defæcate. This is known as the *gastro-colic reflex*. At the end of the rectum is the anal canal, closed by a strong internal sphincter (a thickening of the involuntary circular fibres of the muscular coat), and by the external sphincter, which is a voluntary muscle made of transversely striated fibres.

The "call to defæcation" having been thus produced, the act itself is started by the increase in intra-abdominal pressure brought about by the voluntary contraction of the abdominal wall, the diaphragm and relaxation of the levator ani. The diaphragm is kept down by deep inspirations, followed by closure of the glottis; this depresses the colon, so that the shadow of its transverse portion and the flexures may be lowered as much as 2 inches. The transverse colon may not rise to its normal position until even an hour has elapsed from the act of straining during defæcation. Accompanying the action of these voluntary muscles, the whole colon from the cæcum onwards enters into powerful peristalsis; the contents of the transverse colon are thus forced into the descending colon, from which they are evacuated together with the fæces already present between the splenic flexure and the anus. The entrance of more fæces into the rectum until they reach the anal canal irritates afferent nerves in the wall of the rectum; the nerve impulses so generated pass to a centre or centres in the lumbo-sacral region of the spinal cord, where efferent impulses are set in action upon which depend the reflex acts required to complete the process; these are:—

1. Strong peristalsis of the whole colon.
2. Continued contraction of the abdominal muscles.
3. Relaxation of both the anal sphincters and of the levator ani.

The last traces of fæces are expelled by voluntary contractions of the levator ani.

If the call to defæcation is resisted, the desire soon passes away, and may not recur until the next regular period arrives for the opening of the bowels, twenty-four hours later. It seems likely

that a reverse peristalsis may occur in the lower colon when hard masses of fæces are present. This is suggested by the fact that a foreign body (an egg-cup inserted to arrest bleeding from piles) has been known to travel up to the splenic flexure whence it was removed surgically.

The terminal portion of the large intestine like the rest of the gut has an intrinsic nervous plexus and shows peristaltic movement. When the rectum contracts the internal anal sphincter relaxes (R. C. Garrey). This reciprocal movement as in other parts of the intestine can occur after severance of all connections between the colon and the sacral region of the spinal cord. Normally this expulsive movement of the colon is augmented by a spinal reflex of which the afferent and efferent paths are in the sacral nerves (Garrey). In addition the colon and rectum are inhibited by the sympathetic which inhibits the gut generally and causes contraction of the internal anal sphincter. Excessive sympathetic action (or deficient parasympathetic action) may lead to a severe form of constipation which can be relieved by section of the sympathetic nerves.

The voluntary muscles concerned in defæcation, namely, the external anal sphincter and the levator ani, are supplied by the fourth sacral nerve, which arises from nerve-cells in the conus medullaris of the spinal cord. If the lower part of the spinal cord is destroyed, defæcation still occurs but it is an unconscious act, and the reflex is imperfectly executed, since, as we shall see, the parasympathetic control is interfered with, the destruction of the conus medullaris prevents the normal reflexes taking place in which the levator ani and external sphincter are concerned, and the paralysis of these voluntary muscles may lead to incontinence of fæces.

We thus see that the lowermost portion of the alimentary canal resembles its uppermost portion (pharynx and œsophagus) in being more under voluntary nervous control than is the small intestine. Autonomy at the rectal and anal portion is for obvious reasons undesirable.

Constipation.—Great discussion has taken place regarding the normal frequency of defæcation. Some insist, and they are supported extensively by the many vendors of purgatives, that the bowels should empty daily, but there are many apparently normal persons in whom this only takes place once or twice a week, and instances of much longer intervals have been recorded (see Hurst). In this connection it should be recalled that food residues form but a very small proportion of what is excreted. There is, however, no doubt that the activity of the large intestine is stimulated by the taking of bulky indigestible substances such as the cellulose of fruit and vegetables, but the husk of cereals (bran) is much more effective,

possibly because usually more cellulose is actually taken and there is more stimulation of the mucous cells. It is claimed that the vitamin B of the bran has a beneficial effect in toning up the bowel. In many instances of constipation the colon is in a state of excessive tone sometimes from too frequent indulgence in purgatives. The latter should only be taken as temporary alleviants for eventually they only aggravate the condition.

Neglect is one of the commonest causes of constipation, for the retained faeces continue to lose water, and get harder, and more difficult to expel. Constipation is a possible cause of many—according to some, the majority—of human ailments, because of the absorption of toxic products of putrefaction. There is, however, evidence that mere distension of the rectum and colon may bring about some of the symptoms commonly attributed to constipation (Alvarez).

REFERENCES.—Garry, R. C., 1934; Hurst, 1923.

THE NERVOUS CONTROL OF THE ALIMENTARY CANAL.

We have already seen in relation to peristalsis that such movement is largely independent of external nerves. The activity of the alimentary canal is brought into relation with the general requirements of the body by means of two sets of nerves: the sympathetic and the parasympathetic (vagus and *nervi erigentes*).

The Sympathetic supply leaves the spinal cord by the anterior roots of the spinal nerves. Those for the stomach leave by the fifth to the eighth thoracic roots and have their cell stations in the coeliac ganglia, which they reach by the splanchnic nerves; those for the small intestine by the sixth thoracic to first lumbar roots, but do not synapse until they reach—by way also of the splanchnic nerves—the superior mesenteric ganglion; those for the large intestine by the lower thoracic roots pass down the sympathetic chain to the lesser splanchnic nerves and eventually synapse in the inferior mesenteric ganglion, thence they pass by the colonic nerves to the colon, and by the hypogastric nerves to the rectum and anal sphincter. The eventual distribution of the nerves is with the larger arteries.

The Parasympathetic.—The upper part of the alimentary canal is supplied by the vagi nerves, as far as the middle of the transverse colon, and the large intestine downwards by the *nervi erigentes* or pelvic nerves, which arise from the second, third, and fourth sacral nerves. These are all pre-ganglionic fibres which synapse in ganglia in the intestinal wall, as may be shown by the action of nicotine, which, if painted on the intestine, paralyzes vagal but not sympathetic action.

Local Distribution of Nerves (fig. 164).—In the intestinal wall there are two large interconnected nerve plexuses, one submucous, *Meissner's* (Pl.s.m.), and one between the two muscle layers, *Auerbach's* (Pl.m.) The exact relationship of these plexuses has recently been

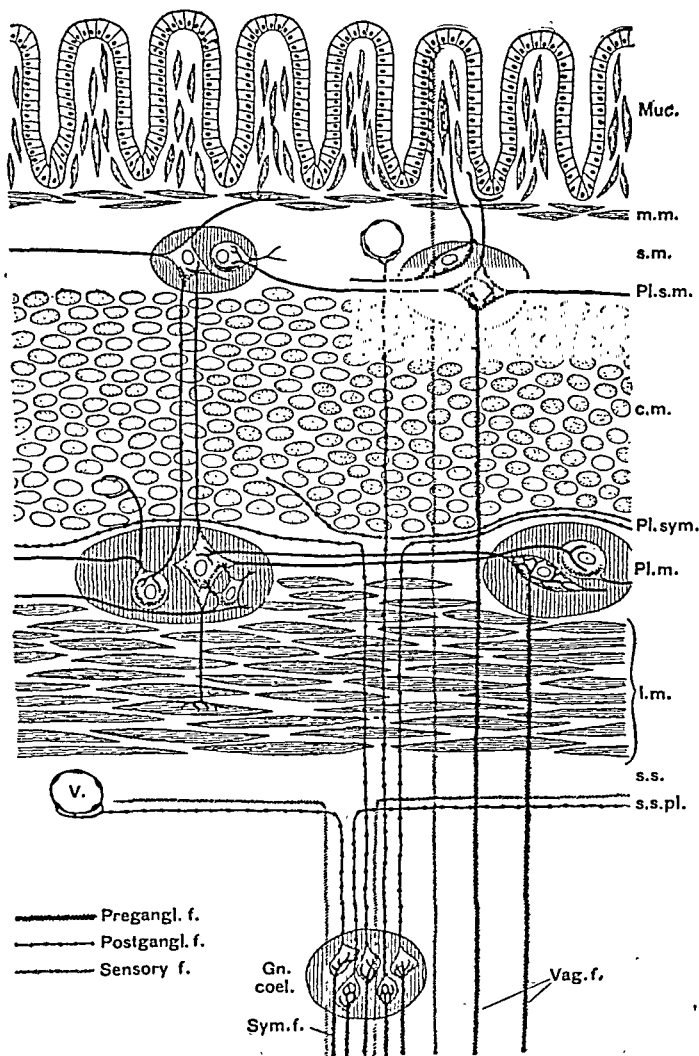


FIG. 164.—Diagram of the nerve supply of the intestine (after C. J. Hill). Described in text.

reinvestigated by C. J. Hill, who has concluded that they are essentially parasympathetic, being concerned in the ultimate distribution of the vagus fibres which we have noted synapse in the ganglia of the plexuses. From the ganglia, post-ganglionic fibres pass to the muscle layers and to a dense *subepithelial plexus* which supplies the villi and glands. The vagal fibres have little or no connection with blood-vessels. It is to be understood that the

so-called plexuses are composed essentially of neurones and are not a nerve network.

In addition to these parasympathetic plexuses Miss Hill has shown the presence of sympathetic plexuses, one intramuscular, from which the muscle cells are supplied, and one subserous, which supplies the serous coat and is probably sensory in function. Minor differences occur in different regions of the gut. Unlike the parasympathetic, the sympathetic fibres are closely bound up with the vessels of the part.

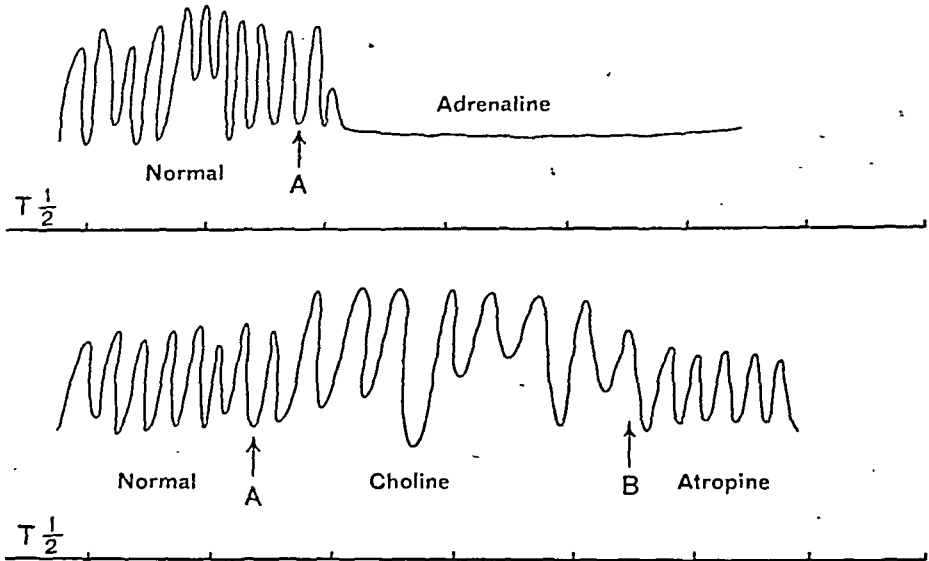


FIG. 165.—The effect of drugs on the isolated intestine in Tyrode's solution by the method shown in fig. 166. In the upper record the inhibiting effect of adrenaline is shown, in the lower the stimulating effect, from A, of choline (like pilocarpine or eserine) which is abolished by atropine, from B. The drugs are dropped into the saline bath and mixed by the oxygen bubbles. Similar records can be obtained by placing a balloon inside the lumen of the intestine and attaching it to a tambour.

The Function of the Sympathetic is generally inhibitory to the movements of the alimentary canal, with the exception of the sphincters and the muscularis mucosæ, which are constricted. The latter are also constricted by adrenaline, the great sympathetic stimulant. Stimulation of the sympathetic or adrenaline causes inhibition of a piece of isolated intestine contracting rhythmically; indeed use is made of this in the biological assay of adrenaline. (See fig. 165.) Excitation of the sympathetic also causes constriction of the blood-vessels of the gut.

It may be assumed that the effect of pain, anger, and severe muscular activity in bringing about inhibition of the gut is exerted through the sympathetic, like the cardiac acceleration caused by similar states.

Function of the Parasympathetic.—This appears to be augmentor and, as we have seen in relation to gastric juice, secretory. The actual effect, for example, of stimulation of the vagus on the stomach has been shown by McCrea to depend on the state of the organ at the time. If it is full, the stomach is contracted, but if empty, it is relaxed. If the intestine is contracting, stimulation of the vagus brings about a brief inhibition, and subsequently marked augmentation, which is caused also by the action of acetyl-choline and pilocarpine, the great parasympathetic stimulants, on isolated intestine. (See fig. 165.)

The action of the parasympathetic normally is most marked during rest, especially that following active muscular exercise, which also facilitates the action of the colon by toning up the abdominal muscles.

Occasionally, especially after the prolonged use of strong purgatives, the large intestine, especially the descending colon, becomes the seat of acute and very painful spasm. This appears to be partly vagal in origin for it is relieved by a large dose of atropine.

The reverse sometimes occurs and the colon dilates to a large size and retains enormous quantities of fæces. The condition is relieved by section of the sympathetic supply (Learmonth).

The movements of the intestine appear to be both increased and decreased by emotional states. It would seem that fear, anger, and exercise diminish intestinal activity at first, but that exercise is followed by increased intestinal activity as it is followed by increased vagal restraint of the heart. An emotion due to a circumstance over which the individual is powerless may have the effect of producing a mass peristalsis and evacuation of the bowels as if the sympathetic was temporarily thrown out of action.*

The secretion of mucus is also markedly affected by nervous stimulation. The secretion of the colon is increased by stimulation of the pelvic nerves especially after eserine and reduced by atropine, but the atropinised colon can absorb fluid completely. Narcotics greatly reduce the rate of secretion of mucus but the effect is combated by eserine. The narcotics therefore probably act on the enteric plexuses (Wright, Florey and Jennings).

The movements of the villi appear to be under the same control as the rest of the activity of the intestine for they are stopped by any procedure which stimulates the sympathetic while they are increased by eserine. The action appears to be under the control of Meissner's plexus (Verzár).

The Study of the Isolated Intestine, etc.—The method of studying the isolated intestine is of special importance, not only because by its use it is possible to investigate the action of drugs

*. This reaction has been commonly observed during air-raids.

on the movements of the intestine itself, but also because the same method is adopted in studying the activity of other structures removed from the body, such as the uterus or strips of blood-vessels. It is by the use of the same apparatus that the biological standardisation of substances, like pituitary extract which acts on the uterus, is carried out.

The organ is placed in a bath of warm oxygenated solution of

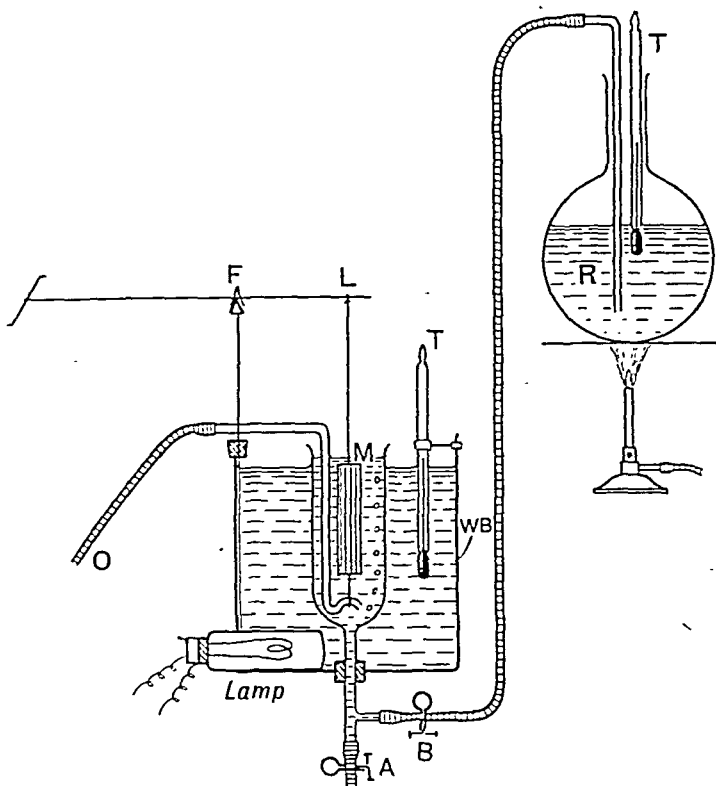


FIG. 166.—*The Intestinal and Uterus Bath* (after Burn).—One end of the organ M to be studied is tied to the bent glass tube through which oxygen is supplied from O. It is lowered into the inner bath of special solution. The other end is tied at L, to a lever which has its fulcrum at F and a frontal glass writing lever (Bayliss). The outside water-bath is kept at body temperature by the lamp. When it is desired to change the fluid surrounding the organ, the bath is emptied by opening clip A and to refill the bath from the warm reserve R, by closing clip A and opening clip B. T, thermometer.

salts, which prevents its normal salts from being removed, and its movements are recorded as indicated by the accompanying figure.

The fluids used are modifications of Ringer's solution which was introduced for the rabbit heart; for the intestine that of Tyrode which contains phosphate and magnesium; for the uterus, bronchi or cat's heart solutions like that of Van Dyke and Hastings, which has less calcium than Ringer's solution, are most suitable.

The detailed composition in percentages is given below but need not be memorised.

	Ringer-Locke.	Tyrode.	Van Dyke and Hastings.
NaCl	0·9	0·8	0 659
KCl	0·042	0·02	0·046
CaCl ₂	0·024	0·02	0·005
NaHCO ₃	0·015	0·1	0·252
Glucose	0·15	0·1	...
MgCl ₂	0·01	0·009
NaH ₂ PO ₄	0·005	0·01
Na ₂ HPO ₄	0·008

Plants may be grown in sand kept moist by similar solutions, with, of course, the addition of other nutrients, *e.g.* nitrates and sulphates from which they form their substance; indeed, such solutions were used for this purpose many years before they were adopted for animal tissues.

REFERENCES.—Alvarez, Barclay, Todd.

CHAPTER XXXIV

INTERMEDIATE METABOLISM

THE word *metabolism* has been often employed in the preceding chapters, and, as there explained, it is used to express the sum total of the chemical exchanges that occur in living tissues.

The living body is always giving off by the lungs, kidneys, and skin the products of its combustion, and is thus always tending to lose weight. This loss is compensated for by the intake of food and of oxygen. For the material it loses, it receives in exchange fresh substances. If, as in a normal adult, the income is exactly equal to the expenditure, the body-weight remains constant. If, as in a growing child, the income exceeds the expenditure, the body gains weight; and if, as in febrile conditions, or during starvation, the expenditure exceeds the income, the body wastes.

The different parts of the body have very different compositions; still, speaking of the body as a whole, Volkmann and Bischoff state that it contains 64 per cent. of water, 16 of proteins, 14 of fat, 5 of salt, and 1 of carbohydrates. The carbohydrates are thus the smallest constituent of the body; they are the glycogen of the liver and muscles, and small quantities of glucose in various parts.

The most important, because the most abundant of the tissues of the body, is the muscular tissue. Muscle forms about 42 per cent. of the body-weight,* and contains, in round numbers, 75 per cent. of water and 21 per cent. of proteins; thus about half the protein material and water of the body exists in its muscles.

The body, however, does not remain in a stable condition; even while nutrition is occurring, destructive changes are taking place simultaneously; each cell may be considered to be in a state of unstable equilibrium, undergoing *anabolic*, or constructive, processes on the one hand, and destructive, or *katabolic*, processes on the other.

The two sides of metabolism may be compared by means of a

* The following is in round numbers the percentage proportion of the different structural elements of the body: skeleton, 16; muscles, 42; fat, 18; viscera, 9; skin, 8; brain, 2; blood, 5.

balance-sheet, and the necessary data for the construction of such a comparison are:—

(1) The weight of the animal before, during, and after the experiment.

(2) The quantity and composition of its food.

(3) The amount of oxygen absorbed during respiration.

(4) The quantity and composition of urine, fæces, sweat, and expired air.

(5) The amount of work done, and the amount of heat developed.

Water is determined by subtracting the amount of water ingested as food from the quantity lost by bowels, urine, lungs, and skin. The difference is a measure of the oxidation of hydrogen.

Proteins.—The nitrogen is derived from proteins, and appears chiefly in the urine. Smaller quantities are eliminated in the sweat and fæces. From the amount of nitrogen so found, the amount of proteins which have undergone katabolism is calculated. Proteins contain, roughly, 16 per cent. of nitrogen; so 1 part of nitrogen is equivalent to 6.25 parts of protein; or 1 gram of nitrogen to 30 grams of flesh.

Fat and Carbohydrate.—By subtracting the carbon in the katabolised protein (protein contains 54 per cent. of carbon) from the total carbon eliminated by lungs, skin, bowels, and kidneys, we get the amount representing fat and carbohydrate, which have undergone katabolism.

Balance of Income and Expenditure in Health.

Tables have already been given of adequate diets; these will in our balance-sheet represent the sources of income; the other side of the balance-sheet, the expenditure, consists of the excretions.

We may select as our example a typical table of this daily exchange of material on an ordinary diet from the work of Pettenkofer and Voit. In the first experiment the man did no work.

Income.			Expenditure.			
Food.	Nitrogen. in gms.	Carbon. in gms.	Excretions.	Nitrogen. in gms.	Carbon. in gms.	Water. in gms.
Protein 137 gms.	19.5	315.5	Urine .	17.4	12.7	1279
Fat . 117 "			Fæces .	2.1	14.5	83
Carbohy- drate 352 "			Expired air	248.6	828
Water . 2016 "		19.5	275.8	2190

Here the body was in *nitrogenous equilibrium*, and it eliminated more water than it took in by 174 grams, this being derived from

oxidation of hydrogen. It stored 39·7 grams of carbon, which is equivalent to 52 grams of fat.

The next table gives the results of an experiment on the same man on the same diet, but who did active muscular work during the day:—

Expenditure.	Nitrogen.	Carbon.	Water.
Urine	17·4	12·6	1194
Fæces	2·1	14·5	94
Expired air	309·2	1412
	<hr/> 19·5	<hr/> 336·3	<hr/> 2700

It is important to notice that the discharge of nitrogen was unaltered, while that of both carbon and hydrogen was increased. At one time protein was considered to be the great source of muscular energy; this was first disproved by an historical experiment made by Fick and Wislicenus on themselves in their ascent of the Faulhorn. The body is most economical in reference to protein waste, and any increase in nitrogenous katabolism which occurs during muscular work is small.

Some observers have found larger changes, notably Cathcart. We may now proceed to study the details and end-results and we may most conveniently consider the question under the three headings of the principal food materials, namely, carbohydrates, fats, and proteins.

METABOLISM OF CARBOHYDRATES.

In plants, carbohydrates are synthesised by the agency of chlorophyll from the simple materials carbonic acid and water, which they take in as foods. The first substance formed is probably formic aldehyde, $\text{H} \cdot \text{CHO}$ (which is the simplest carbohydrate known), and this by condensation is converted into sugar, and finally, into starch. We have no clear evidence that a synthesis of this kind ever takes place in animals, the main source of animal carbohydrate being vegetable carbohydrate.

We have seen that the more complex carbohydrates are broken down to monosaccharides in digestion. By salivary digestion and the amylase of the pancreatic juice, starch is hydrolysed to maltose, which is further converted into glucose by the maltase of intestinal juice. Cane-sugar is inverted by invertase to glucose and fructose while lactose is broken down into glucose and galactose by lactase.

These monosaccharides are absorbed into the blood-stream, but they are rapidly, for the most part, converted into glucose, probably by the liver. In excess they are rapidly excreted by the kidney as abnormal substances. We may then consider glucose as the current carbohydrate coin of the body.

The Utilisation of Sugar.—The sugar may be utilised in three ways: it may be stored as glycogen, in which form it is readily available for reconversion into glucose; or as fat, which is a more concentrated form of storage; or it may be used as fuel that is oxidised in the organs of the body, especially the muscles, whose requirements are most variable. It appears, however, that glucose cannot be utilised adequately for any of these purposes without the co-operation of the internal secretion produced by the pancreas and known as insulin, the action of which will be dealt with further below. (Summary in fig. 168, p. 482.)

(1) *The Formation of Glycogen—Glycogenesis.*—Glycogen appears to be formed whenever the supply of glucose is in excess of that required for immediate use. As we have already seen above, it is a polysaccharide and is much less stable than vegetable starch. About a half is stored in the liver and about a similar quantity in the muscles, but it is present in small amounts in most tissues. Foetal muscle and the auriculo-ventricular bundle are particularly rich. It may be demonstrated in liver cells by staining with iodine which turns the glycogen granules reddish-brown, but in order to show this it is necessary to give the animal a diet rich in carbohydrate and, after killing it, to plunge the tissue immediately into boiling water to fix the liver cells, otherwise the glycogen is very rapidly reconverted to glucose. In the case of the muscles, this condensation of glucose has been demonstrated by perfusing these structures with blood containing glucose, and subsequently estimating the amount which they have taken up. The liver apparently cannot make glycogen from glucose in this way, but only if lactic acid or fructose solutions are perfused. The storage is therefore not so simple as at first sight appears for the liver cannot make glycogen from the blood glucose. For the storage of glycogen by any organ the presence of insulin in the blood is necessary. The liver of a well-fed man has been calculated to hold about 200 grams.

Actually the demonstration of glycogen storage in the liver was one of the earliest experiments done on carbohydrate metabolism. Claude Bernard, in 1848, washed a liver apparently free from glucose, but on letting it stand for an hour found that glucose again appeared in the perfusate, thus showing that there was in the liver a precursor of glucose. Bernard, however, considered that the liver secreted glucose and first used the term "internal secretion" in this connection.

He also went further, he washed the liver free from glucose, cut it up and threw it into boiling water in which he ground it. After filtering off the solid material he found he had an opalescent solution from which he was able by means of alcohol to precipitate

a substance which he called glycogen (the sugar former). Bernard was Professor of Physiology in Paris.

As we shall see, the rapid conversion of glycogen into glucose is of great value when large amounts of fuel are needed in the blood. The glycogen in the muscles, which in man is about 350 grams, is immediately available for muscular exercise; but apparently in the mammal, if it is broken down into lactic acid and not actually needed, it is again built up into liver glycogen. The total glycogen stored in the body is about 600 grams and will supply about 3000 calories, or sufficient for one day. Liver glycogen may also be formed from protein if more of this substance is taken in than is needed for the repair of tissue. Some workers believe that it may also be made from fat, but the evidence on this point is not complete.

Glycogen never disappears completely from the liver in starvation, but may do so in strychnine convulsions or after injection of phloridzin which causes excessive loss of glucose from the kidney.

(2) *The Formation of Fat.*—That fat can be formed from carbohydrates was definitely proved by the well-known experiment of Lawes and Gilbert, in 1852, on the fattening of pigs by feeding them with barley. This transformation has never been accomplished outside the body and its possibility was at first denied by chemists. How the long chains of the fat are linked together from the shorter carbohydrate chains is difficult to see. Micro-organisms can accomplish the change of lactic acid into such fatty acids as acetic, butyric and caproic; boiling with alkali brings about a similar reaction. The most recent view is that pyruvic acid or acetic aldehyde may be the intermediate state, but all we can say is that the change probably takes place in the liver.

(3) *The Formation of Lactose, etc.*—In the lactating mammal the mammary glands produce lactose from glucose, presumably through galactose.

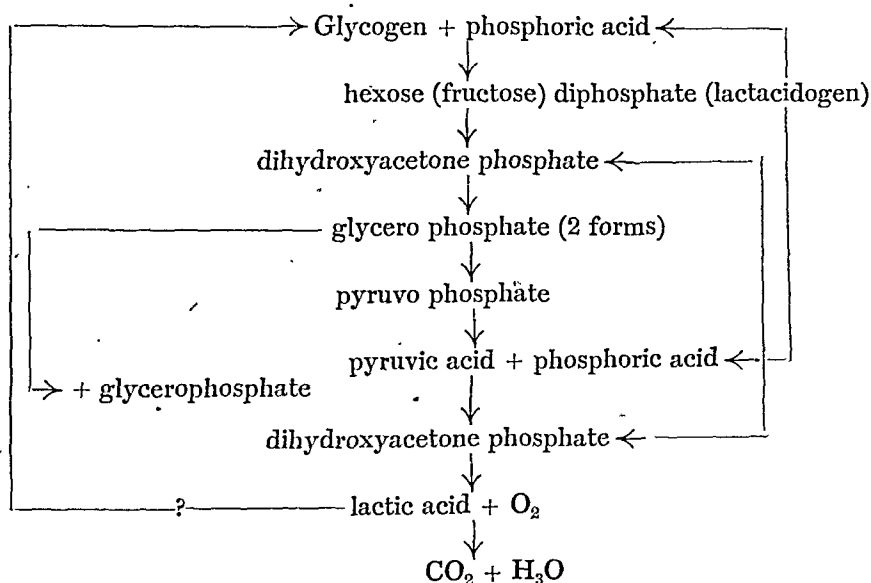
In certain circumstances glucuronic acid is elaborated from glucose for the detoxication of poisonous substances to be excreted in the urine, and these give the tests for glucose. In other circumstances pentoses are formed.

(4) *Oxidation of Carbohydrates.*—All carbohydrates are oxidised eventually to carbon dioxide and water, but it is now known that many intermediate stages occur. Lactic acid is the best known and most easily recognised intermediate product, but there are many others.

The first stage appears to be the combination with phosphoric acid or phosphorylation of the glycogen to form a hexose phosphate. In support of this view, it is found, for example, that the addition

of phosphate to minced muscle causes all the glycogen store and even added glycogen and glucose to be converted into lactic acid. Such a substance as hexose phosphate is found in the muscle juice and can be converted into lactic acid and phosphate, and these are found in equivalent amounts. Substances, *e.g.* arsenites, which hasten the decomposition of hexose diphosphate in yeast fermentation, hasten the oxygen consumption and lactic acid formation in muscle. It is known, also, that muscular work increases the amount of phosphate excreted.

The origin of the phosphoric acid appears to be adenylyl pyrophosphate and indirectly creatine phosphate (see Chemical Changes in Muscle, p. 41), sometimes called phosphagen, because of this action. If adenylyl phosphate is removed from muscle juice the reaction does not proceed, although all the other constituents necessary are present. Detailed investigation has revealed several stages in which phosphoric acid plays a part thus:—



It is known that most tissues contain oxidation and reduction enzymes, which can break down such substances generally (see Tissue Respiration). These stages, especially the pyruvic acid stage, are important as they may be common points in the breakdown or synthesis of carbohydrates, fats, and proteins.

REFERENCES.—Schaffer and Ronzoni, Cori, Needham, Robison.

The Relation of the Pancreas to Carbohydrate Metabolism.

The fact that the pancreas was related to carbohydrate metabolism was first demonstrated by Minkowski and von Mering in

1889, who removed the pancreas in dogs. It was observed that the dogs licked their urine and this led to the discovery of the presence of glucose in the excretion; further, that the glycosuria did not develop if a small piece of pancreas was transplanted under the skin and that otherwise total removal of the pancreas resulted in death in a few weeks. A year later Schultze showed that mere tying or blocking of the pancreatic duct did not produce such symptoms, which soon became recognised as the same condition as diabetes mellitus in man, in which the pancreas was known often to be diseased. These experiments led to the discovery that the islets of Langerhans which, unlike the ordinary acinar cells, do not degenerate when the ducts are tied, produced a substance which controlled carbohydrate metabolism. This substance was called *insulin* by de Meyer in 1909. The steps leading to its actual discovery are given by Macleod, 1926.

The Preparation of Insulin.—The knowledge of the subject remained almost stationary for thirty years, although spasmodic unsuccessful attempts were made to make extracts of pancreas, which would alleviate the condition of diabetes, until Banting and his colleague Best demonstrated conclusively that there was a substance in the pancreas which could cause the glycosuria to disappear, but that the activity of extracts was usually destroyed by the pancreatic trypsin. They found it possible to make potent extracts from the pancreas of foetal calves in which trypsin was not yet formed and from animals in which the trypsin-producing cells had been caused to degenerate by previously tying the duct.

Subsequently it was realised that trypsin is insoluble in 50 per cent. alcohol, and this was the basis of the original method of extraction. Extracts are now made with cold weak alkaline alcohol and precipitated by adding further alcohol or by grinding up the pancreas with solid picric acid which precipitates the protein and insulin and redissolving the latter with acetone. (Collip; Dudley; Dodds and Dickens.) Insulin is now used extensively in the treatment of diabetes. Thus out of the early experiments, carried out on animals in the cause of pure science, an enormous benefit has been conferred on mankind.

The amount of insulin in the pancreas is reduced by a fatty diet and by fasting. A low carbohydrate and high fat diet renders a subject more sensitive to insulin through an action on the pituitary body (Himsworth). Insulin causes a secretion of gastric juice and is used instead of a test-meal in studying gastric secretion. It is excreted by the kidney.

The Chemistry of Insulin.—The exact formula of insulin has not yet been worked out, as it is a complex protein, but it has been possible to prepare it in crystalline form, zinc being apparently

necessary for the crystallisation (Abel, Harrington and Scott). Insulin contains most of the common amino-acids but no tryptophan. It is not stable in alkaline solution, although fairly so in acid.

The *standardisation of insulin* was originally carried out by determining how much insulin was required to lower the blood sugar to 0.04 per cent. when convulsions are produced in a fasting rabbit of 2 kilos. It is now standardised by comparing the activity of the unknown sample with that of a standard sample agreed upon by a League of Nations Committee.

One milligram of the crystalline substance is equivalent to 24 units.

The Nature of Insulin Action.—We have seen that insulin facilitates the utilisation of carbohydrates. It has also been shown, by Hawley and Murlin, that the oxidation of sugar is markedly increased, although, during the first hour, in insulin hypoglycæmia the sugar is apparently built up into some other substance. Exactly what happens to the glucose under the action of insulin has been shown by the experiments of Best, Dale, Hoet, and Marks, who perfused for a long period a glucose solution, plus insulin, through the vessels of an animal in which the alimentary canal and its associated glands including the liver, had been removed. They found that all the glucose which had disappeared could be accounted for by oxidation or by increase of muscle glycogen.

We may, then, look upon the action of insulin as increasing the activity of tissues in relation to carbohydrate, whatever that action may be. • Thus it facilitates the building of glycogen by the liver and muscle and its utilisation by the muscle. When the blood sugar is high in a diabetic the injection of insulin causes, therefore, glycogen to be built up in the liver, but by facilitating glucose usage in the enormous mass of body muscle it may cause the blood sugar to fall below normal. The intimate nature of the action of insulin is still a problem.

Hypoglycæmia (Low Blood Sugar).—If insulin is injected into a normal animal (or in excess into a diabetic animal) the blood sugar falls. When, as has been said, it has fallen in rabbits to 0.04 per cent., convulsions ensue; but this level is not usually reached unless the animal has been starved for twenty-four hours to get rid of the glycogen store. As this store is never quite depleted the convulsions may cause a temporary rise of blood sugar.

In man, a similar state occurs, but it is commonly initiated by hunger, sweating, loss of emotional control (parasympathetic activity?), faintness, and lassitude.

An excessive dose of insulin causes (like oxygen-want) uncon-

sciousness and eventually death from respiratory failure as a result of the loss of fuel supply to the brain, since there is nothing to oxidise. Complete recovery occurs, however, when the fuel is restored by the injection of glucose or is mobilised by adrenaline (see below). Posterior pituitary extract also acts, but apparently by antagonising the insulin, for it does not raise the blood sugar. Hypoglycaemia and increased sugar usage are common in some forms of pituitary disease, presumably as a result of the absence of this antagonising action. Individuals vary very much in their sensitivity to insulin, as is indicated by the speed of the fall in blood sugar.

Cases have been recently described in which hypoglycaemia is due to a local overgrowth (adenoma) of the islet tissue of the pancreas.

The Mechanism of Insulin Secretion.—Just as the external secretion of the pancreas is controlled by the vagus nerve, so also is the internal secretion. Stimulation of the peripheral end of the vagus, the injection of pilocarpine or of alkali (which has many other actions like those of the parasympathetic) all cause a fall of blood sugar. In order to demonstrate this, however, it is necessary to paralyse the sympathetic with ergotoxine (Clark), or to stimulate the sympathetic previously to a maximum. These facts suggest that whatever the nature of insulin action it acts during the time when the parasympathetic is most active, *i.e.* during physical and mental rest. Of some significance may be the fact that when a diabetic is in the habit of taking exercise, less insulin is necessary, and we know that in the intervals between exercise there is often increased parasympathetic activity. It appears that insulin is normally circulating in the blood, since the transfusion of normal blood brings about a lessening of blood sugar in a diabetic, and its presence normally in the tissues is indicated by the fact that there is less blood sugar in the venous than in the arterial blood. This is not so in the diabetic (Lawrence).

There is some evidence also that the ingestion of carbohydrate causes an outpouring of insulin. If a quantity of glucose (100 gms.) is administered to an individual there is a rise of blood sugar which is followed by a fall below the resting level. At this stage a subsequent similar dose of glucose may not cause the blood sugar to rise.

It has also been shown by Glen that the venous blood of a dog injected with glucose will reduce the blood sugar of another dog. On the other hand, many workers have failed to find that the injection of glucose into the blood causes any increased speed in the fall of blood sugar after a second injection.

The Maintenance of the Blood Sugar Level.

The Blood Sugar.—This term is given to the glucose present in the blood and the amount depends on the balance between the amount of sugar being absorbed and that being utilised, stored, or lost. Usually it does not sink below the level, 0·08 to 0·1 per cent. nor rise above 0·18 per cent., the renal threshold value. A normal individual should, however, be able to consume 150-200 grams of glucose without any appearing in the urine (*i.e.* the normal sugar tolerance).

The Blood Sugar Curve.—In studying carbohydrate metabolism in man it is customary to make a graph of the rise of blood sugar following the ingestion of 50 grams of glucose in water flavoured with lemon (fig. 167).

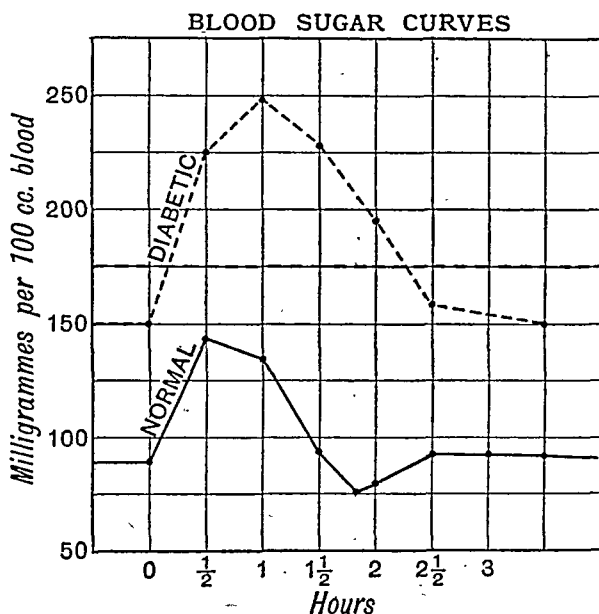


FIG. 167.—The curves show the effect of taking 50 grams of glucose on the blood sugar of an average normal and average diabetic subject. There is, however, considerable individual variation since the curve is the result not only of the speed of utilisation of the sugar, but also on its speed of absorption from the intestine, and on the dietetic habits of the subject.

The actual shape of the curve depends largely on his dietetic habits. A subject who normally takes large quantities of carbohydrate has therefore a comparatively small and short-lived rise of blood sugar.

Estimation of Blood Sugar.—The method of McLean which is much used consists in principle in the precipitation and removal of the protein by heat and colloidal iron. The filtrate is boiled with alkaline copper salt solution containing also potassium iodide and

iodate. The sugar reduces the copper which is re-oxidised by the iodine. The determination by titration with sodium thiosulphate of the iodine used gives the amount of copper reduced and thus of the glucose present.

If there is excessive utilisation of glucose by the muscles, or the blood sugar falls from any other cause, the body calls on its reserve of carbohydrate, stored in the form of glycogen, especially that of the liver, to maintain the blood sugar level.

Hyperglycæmia (High Blood Sugar).—This occurs whenever the amount of sugar absorbed is in excess of that utilised or stored, and may be produced in a large variety of ways. It occurs, as we have seen, if the pancreas is out of action and the carbohydrate utilisation is reduced, if excessively large quantities of carbohydrate are eaten or when more sugar is mobilised than is actually used. This latter hyperglycæmia depends on the presence of a glycogen-laden liver.

Glycosuria.—This results whenever there is a hyperglycæmia *i.e.* blood sugar above the *renal threshold* which commonly varies in different individuals from 0.10 to 0.20 per cent. In being excreted the sugar takes with it a large amount of water; the glycosuria is therefore accompanied by a polyuria (increased production of urine). A few otherwise normal persons have a so-called renal glycosuria, because of a lowered renal threshold, but the condition is not serious. Experimentally, this threshold can be lowered by the injection of phloridzin. This glucoside acts apparently by impairing the normal function of the kidney, since, if the kidneys are tied off, the blood sugar instead of falling rises. Also, if the substance is injected into one renal artery, sugar appears first in the urine of the same side, thus showing the local action of the drug on the kidney. This is believed to be a poisoning of the phosphorylating mechanism of the tubules upon which the reabsorption of sugar depends. It must, however, be realised that the term "renal threshold" is a convenient one which depends on two factors, the permeability of the capillaries of the kidney glomeruli, and the power of absorption by the renal tubules. In diabetes more sugar is filtered off than the tubules can reabsorb. (See the Function of the Kidney Tubules.) As a result of the fall of blood sugar the glycogen of the liver is depleted and later sugar is made from protein to maintain its level in the blood.

The Mobilisation of Glucose (Glycogenolysis).—It has long been known that the amount of glycogen in a muscle diminishes if it is made to contract, and that immediately after severe exercise the blood sugar is high, and there may even be glycosuria. Further, it is found that in severe muscular work the respiratory quotient over the total period of the work is nearly unity, indicating that more carbohydrate has been consumed. It is, therefore, to be expected

that a mechanism for the rapid mobilisation of glucose exists and, indeed, much of the older work in relation to glycosuria, as we now realise, supports this view.

The essential facts were first made out by Claude Bernard, to whose work we have already referred. These observations have been amply confirmed by the work of Mann and Magath, who have shown that many procedures which cause an increase in blood sugar, *e.g.* the production of asphyxia or the injection of adrenaline, fail to do so if the liver has been previously removed.

This mobilisation of glucose, accompanied by the reduction of liver glycogen, takes place not only in exercise, but also when a fall of blood sugar is produced experimentally by the injection of insulin which, as we have seen, causes a transference of the sugar to the muscles. Once glycogen has been transferred to the muscles it apparently ceases to be available for use by any other organ, even in starvation (Cori).

The actual glycogenolysis, or glycogen breakdown, is a hydrolytic process, like the breakdown of starch, brought about through the agency of two enzymes. The first, phosphorylase, in the presence of its co-enzyme adenylic acid causes the glycogen to take up phosphoric acid with the formation of glucose-phosphate, from which glucose is liberated through the agency of the second enzyme, phosphatase. The reaction is governed largely by the amount of the reacting substance present and by the hydrogen-ion concentration of the medium in which it acts. It is most active just on the acid side of neutrality. The enzymes may be looked upon as being responsible for the breakdown of glycogen, which occurs rapidly at death, and as facilitating that which, as we shall see, occurs in asphyxia.

The glycogen in the muscles is converted, not into glucose like that in the liver, but into lactic acid, thus probably saving two stages in the breakdown process. The chemistry of the processes is discussed in relation to Oxidation of the Carbohydrates.

The total glycogen reserve of the body is calculated at about 400 gms. in a well-fed man; that is sufficient to produce about 2000 calories or sufficient energy for half a day's moderate physical work.

The Causes of Mobilisation.—This has been investigated largely by studying the various procedures which cause hyperglycæmia and glycosuria. It might be expected from what has been said that the mobilisation is under sympathetic control, and there is a certain amount of evidence to indicate this. This view would appear to be supported by the classical experiments of Claude Bernard, who found that puncture of the floor of the 4th ventricle resulted in glycosuria, and that this did not occur if the nerve path-

ways between this point and the liver were cut. Unfortunately, these experiments tend to be complicated by interference with respiration and a fall of blood-pressure, which themselves affect the blood sugar, and they are therefore not so conclusive as at first thought.

Stimulation of the splanchnic and hepatic nerves also causes hyperglycæmia, but Macleod suggests that this result is due to the stimulation of the suprarenal glands and the outpouring of adrenaline, since he found that if these glands were removed the hyperglycæmia no longer occurred. On the other hand, it has been found that if the hepatic nerves are cut, splanchnic stimulation no longer causes hyperglycæmia, a fact which indicates

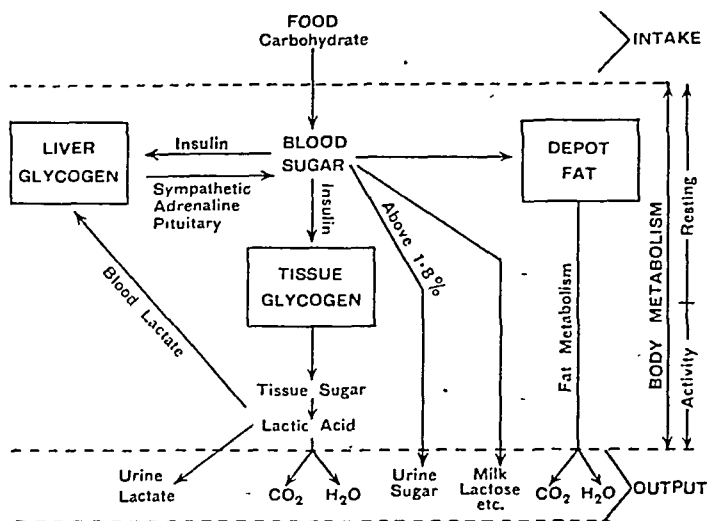


FIG. 168.—Diagrammatic summary of carbohydrate utilisation and its control.

intimate nervous influences. The exact control is, therefore, still a matter for decision. That the mobilisation of glucose is under sympathetic control appears certain and the view is supported by the fact that a very large number of conditions which increase sympathetic activity generally cause hyperglycæmia. Of special importance is the action of adrenaline (extract of suprarenal gland) which, when injected, causes a hyperglycæmia by reducing the glycogen content of the liver. It also converts the glycogen of the muscles into lactic acid, which is then converted into glucose by the liver. This does not, however, occur after the injection of ergotamine which paralyses the sympathetic. Asphyxia causes a similar hyperglycæmia, and any drug which depresses the respiratory centre acts likewise. Similarly, sensory stimulation and, as we have said, severe exercise cause hyperglycæmia.

Mobilisation of glucose from the liver is facilitated by the action

of the thyroid, as is seen by the fact that feeding with thyroid increases the hyperglycæmia produced by adrenaline, and lessens the hypoglycæmia caused by insulin. Hyperthyroidism in man produces hyperglycæmia, and, as we shall see, so does increased activity of the posterior lobe of the pituitary body.

The recent observation by Houssay that hyperglycæmia does not occur if the pituitary body is removed at the same time as the pancreas, suggests that this organ has an intimate relation to sugar usage.

Diabetes Mellitus.—The term *diabetes mellitus** is given to disease of the pancreas, which leads to a typical reduction of capability to utilise carbohydrates, with hyperglycæmia and glycosuria as a result. The excess of sugar in the urine takes with it water and brings about an excessive production of urine which, together with the fuel loss, leads to great thirst and appetite. There is at the same time greatly impaired vitality, with increased liability to infection. Diabetes may arise from chronic inflammation of the pancreas by its being poisoned by various substances, but some cases arise so early in life that a congenital abnormality may be suspected.

Experimentally, a similar result is produced by removal of the pancreas. After removal of the organ, the blood sugar may rise from its normal 0.08-0.11 to 0.2-0.4 or more in twenty-four hours. Diabetes due to degeneration of the pancreas may also be produced by the injection of a number of substances such as alloxan and extracts of the anterior lobe of the pituitary. These methods are convenient for experimental use and are of special interest as some cases of diabetes occur which are not responsive to the injection of insulin.

The rise of blood sugar is certainly due to under-utilisation, but since in diabetes removal of the liver causes a fall of blood sugar, even if the liver has been previously exhausted of glycogen by starvation (Mann and Magath), we must assume that the hyperglycæmia of diabetes is in part due to an excessive action of the liver in forming sugar. A study of the ratio of dextrose to nitrogen excreted in the urine (*D:N ratio*) suggests that in the diabetic, sugar is formed from protein.

As a result of the faulty combustion of carbohydrates, the organism uses fat in excess to provide energy, but it would seem that some of the ketone bodies produced by the liver are liberated faster than they can be used, with the result that a fatal acidæmia in ketosis results. (See The Oxidation of Fats.) In the treatment

* This condition is not to be confused with *diabetes insipidus*, a disease produced by disease or injury to the pituitary body or hypothalamus, characterised by the passage of large quantities of very dilute urine *not* containing sugar. It is discussed later.

of diabetes glucose is commonly given with the insulin to prevent hypoglycæmia, but should the latter ensue it may at once be relieved by the administration of glucose, adrenaline, or pituitary extract. Modern views on the mechanism of diabetes mellitus are summarised by Himsworth, 1939.

Metabolism of Fats.

The chemistry of fats has already been considered.

The Origin of Fats in the Body.—The fats in the body arise from two main sources, namely, the fat and also the carbohydrate of the diet. We have already referred, in relation to the metabolism of carbohydrate, to the classical experiment of Lawes and Gilbert, who demonstrated that pigs could be fattened on a diet consisting chiefly of carbohydrate—barley. They found that the fat formed was greatly in excess of the small quantities unavoidably given in the food. It was considered by Voit and Pettenkoffer that, since they could fatten dogs on lean meat, fat was probably formed from protein, and on theoretical grounds this seems possible, since, as we know, the non-amino part of amino-acids may be utilised as fuel. At the time, the experiments were not accepted as conclusive, because the glycogen and fat of even lean meat had not been sufficiently considered. The later work of Atkinson, however, supports the earlier view, that smaller amounts of protein lead to an accumulation of glycogen and in exceptional circumstances feeding on *large* quantities of protein with water and salts may lead to an accumulation of fat as well.

As we have seen in relation to digestion and absorption, fat is taken up by the villi partly as fatty acid and glycerol and partly also as neutral fat. However absorbed, it appears in the lacteals as neutral fat. Thence it passes by the thoracic duct to reach the left innominate vein. Only 60 per cent. of the fat taken can, however, be recovered from the thoracic duct and no satisfactory account for the remainder has yet been offered. It may be stored locally, or may be absorbed into the blood. If the latter, it must be removed at once, as the blood fat does not rise if the thoracic duct is tied.

The Blood Fat.—Like the blood sugar, the blood fat rises after a meal and may reach a maximum of 2 per cent. about six hours later. A little later there is an increase of the lecithin and cholesterol of the blood. In disease, *e.g.* diabetes mellitus, in which fat metabolism is disordered or excessive, the blood fat may rise even to ten times the normal maximum.

How the blood fat is controlled is not clear. It is maintained at its normal level in spite of complete starvation for many days, when the fall of the R.Q. indicates that fats are the chief source of energy.

The Utilisation of Lipides.—The fat is burnt as fuel, or it is stored in the fat depôts of the body and acts as reserve stores of energy. In the lactating mammal it is secreted in the milk.

Fat appears also to be a constituent of cells, for even in starvation it is never absent and may be stained. Although it may not be seen normally it becomes evident microscopically in the pathological states known as fatty degeneration. This is sometimes known as the constant fat, as distinct from the variable fat of the depôts. It is valuable also as insulating material, and those animals which live in cold environments have usually large amounts of subcutaneous fats. We have already seen that it is the normal vehicle of vitamins A, D, and E.

The more complex lipides such as the phospholipide lecithin (see p. 275) have probably other functions.

It has been suggested that lecithin is formed from the blood fat and that it has special importance in relation to the transport of fat in the body (Bloor). It would be well suited for this purpose, as it is the only non-toxic compound of the fatty acids which is miscible with water and is easily formed from fatty acids. He also suggests that the fat is converted into phospholipide before being desaturated. (See Bloor, 1939; also Sinclair, 1934.) The corpuscles of the blood contain more cholesterol and lecithin than the plasma, but it is not known what significance this fact may have. It has been suggested, from observations on the tail fat of the tadpole, that the leucocytes have some special function in transport, since they have been seen loading and unloading themselves. It is probably a constituent of all cell membranes and plays a part in permeability and surface phenomena.

The **storage of fat** takes place in the liver and in that variety of connective tissue known as adipose tissue which occurs specially below the skin and in the omentum and mesentery; in the cells of adipose tissue the fat is present in the form of large droplets, fluid at body temperature. These deposits are known as the fat depôts.

Normally, the fat which is built up by an animal is peculiar to that animal, but if it is starved and subsequently fed on fat unusual to its diet, it may put on fat of another composition. The different fats can be readily identified by their melting-points and their iodine values. (See Chemistry of Fats.)

When, therefore, an animal takes a fat different in composition from its own fat, the appropriate fatty acids are added or taken away before the fat is deposited. We must presume, in the absence of more exact knowledge, that the additional fatty acids are specially made for this purpose from the carbohydrates of the diet. Munk further discovered the remarkable fact that if fatty acids are given as food the chyle contains fat, the glycerol

having been added by the intestine. Only a limited amount of glycerol is, however, available for this purpose since if fatty acids are given only part is absorbed. The fat which is made from carbohydrate is that peculiar to the animal.

The normal neutral fat of the depôts contains 95 per cent. of saturated fatty acids. The liver fat, on the other hand, is usually much more unsaturated than that of adipose tissue and this appears to be of special significance in the preparation of fat for final combustion. (See Drummond, 1933.)

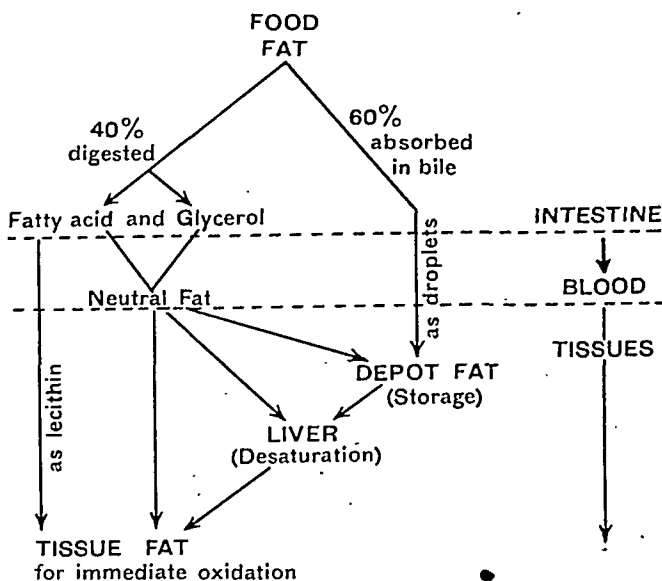


FIG. 169.—Diagrammatic summary of fat metabolism.

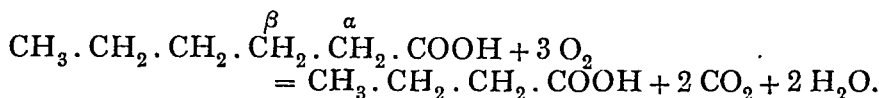
The amount of fat in the liver is greatly reduced by adding choline to the diet, but the mechanism of this lipotropic action and its significance is unknown. (Best, 1934.)

This storage of fats in the depôts is most important, as fat is a most economical form of fuel, or source of potential energy. The storage of 100 calories may be effected in a space of 12 c.c. of adipose tissue weighing 11 grams, the storage of the same amount of potential energy as glycogen is never effected in less than ten times that bulk of liver tissue weighing 130 grams, and rarely in less than double this amount. If the formula of a fat is compared with that of a carbohydrate, it will be observed that fat is relatively deficient in oxygen, and when it has to be burnt it requires more oxygen than a carbohydrate. Hence it is that a gram of fat has a higher calorific value (9.3) than carbohydrate (4.1) and that the burning of fat is accompanied by a lowering of the respiratory quotient.

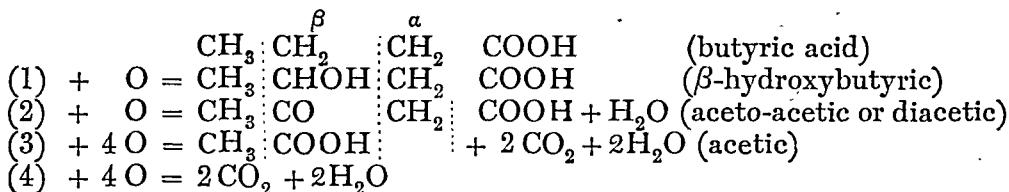
The fat which is stored is quite different from that which is part of the make-up of the cells themselves. The latter is not used up even in starvation but is kept available for muscular exercise.

The destinations of fat in the body are indicated by fig. 169, p. 486.

The Oxidation of Fats.—Although we know that fats are eventually oxidised to carbon dioxide and water, the intermediate steps are as yet by no means certain. A considerable amount of evidence has, however, accumulated to the effect that the long chain fatty acids are first oxidised to smaller chains. Thus caproic acid becomes butyric acid, and so on until CO_2 and H_2O are reached.



We may indicate, as suggested by Knoop, the reactions which take place in the metabolism of butyric acid thus:—



Although, however, this oxidation is shown occurring in stages it must be understood that the reactions all occur together.

That the long chain loses two carbon atoms at once from the end where the COOH group is attached (β -oxidation), is suggested by the following experiments. Advantage is taken of the fact that the body cannot break down the benzene ring. An artificial fatty acid containing this ring is made and administered to an animal. The fatty acid chosen may have an even or an odd number of carbon atoms; one with an odd number is more completely oxidised than one with an even number, further oxidation being prevented by the formation of a stable end-product. Thus from a fat with an odd number, the end-product benzoic acid ($\text{C}_6\text{H}_5\text{COOH}$) is produced; from a fat with an even number the substance phenylacetic acid ($\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{COOH}$) is the end-product. The end-product in each instance combines with glycine to form hippuric and phenaceturic acid respectively and as such is recognisable in the urine.

Similarly, Embden and his co-workers have found that in a perfused isolated liver, more acetone is produced when fatty acids with an even number of carbon atoms are added to the blood than when one with an odd number is added. This can be explained if oxidation results in the removal of two carbon atoms at a time from the fatty acid. When only four carbon atoms are left, butyric

acid is formed and this is known to give rise to acetone under these conditions, whereas propionic acid, which would be derived in the same way from an acid with an uneven number of carbon atoms, does not. In this connection it is of interest that the only fats which the body is called upon normally to metabolise have an even number.

It is interesting also to observe that Dakin has found that oxidation with hydrogen peroxide (which we know is important in biological oxidation) will bring about β -oxidation *in vitro*.

In addition to this type of oxidation it has been shown by Leathes and his co-workers that the liver may convert saturated acids into unsaturated ones (desaturation). This process removes two hydrogen atoms in the middle of the chain and makes it more easily split into two shorter chains. It thus renders them more liable to further oxidation and may represent a preliminary stage in the oxidation of fatty acids. (See Leathes and Raper, 1924.)

Ketosis.—This condition, we have seen, may occur in diabetes mellitus when the tissues are unable to utilise glucose as a source of energy to the normal extent. It is so-called because of the appearance of keto-bodies in the blood and urine, that is of bodies like acetone having a CO-group. In this condition the blood fat may rise to 20 per cent. The exact mechanism of the production of the ketone bodies is a matter of debate. Until recently it has been accepted that when the four-carbon stage is reached (butyric acid) by successive oxidations in the β position, further oxidation appears to be more difficult and to depend in some way on the simultaneous combustion of carbohydrates. If the combustion is deficient as in diabetes, the oxidation of the butyric acid instead of proceeding completely to carbon dioxide and water stops or is delayed at the stages of β -hydroxybutyric acid and aceto-acetic acid. The latter, $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOH}$, readily loses CO_2 forming acetone $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_3$.

In this scheme, however, the odd-numbered fatty acids could not give rise to ketone bodies, but it has now been shown by Jowett and Quastel that such bodies are made to a small extent by slices of liver from fatty acids with an odd number of carbon atoms, *e.g.* valeric ($\text{C}_4\text{H}_9\text{COOH}$) and heptoic ($\text{C}_6\text{H}_{13}\text{COOH}$) acids. McKay and his colleagues have obtained similar results. A more probable view has been put forward, namely, that the ketone bodies are the condensation products of acetic acid molecules which occur during normal oxidation of fat, leaving propionic acid residues (in the case of the odd numbered chains) which condense to form sugar. The feeding of propionic acid* alone results in glycogen being laid down in the liver without ketosis. Acetic acid has also

* Propionic acid, $\text{C}_2\text{H}_5\text{COOH}$, is the next fatty acid below butyric, $\text{C}_3\text{H}_7\text{COOH}$. (See p. 271.)

been shown to increase to a small extent the production of aceto-acetic acid by slices of liver tissue. On the other hand, acetic acid has never been shown to be a product of the normal breakdown of fatty acids.

The most probable view is, then, that ketosis is due to an excessive breakdown of fat (Soskin and Levine) and carbohydrates prevent it by building up the liver glycogen and reducing the importance of fat as a substance for oxidation. This view gains support from the fact that it has never been possible to relate quantitatively the amount of ketosis to the amount of fat and carbohydrate actually burnt, nor has it ever been found that there is any faulty mechanism of β -hydroxybutyric or aceto-acetic acids in the peripheral tissues. It probably explains, too, why ketosis in a fat dog is greater than in a lean one (Best), and why ketosis occurs in starvation.

The ketone bodies are most important in disease. Aceto-acetic acid is particularly toxic, it is thought, because of the enolic form $\text{CH}_3\text{—C(OH) = CH—COOH}$ in which it may occur. It is a general nervous depressant first causing unconsciousness or coma and eventually death from paralysis of the respiratory centre. This danger is reduced by the administration of carbohydrates together with insulin.

The presence of acetone, which gives the breath and urine the characteristic apple-like odour, is not necessarily of serious significance.

It is a remarkable fact that some individuals can consume a very high fat diet, and hibernating animals use their fat without evidence of ketosis, while patients suffering from urinary infections and put on a ketogenic diet of much fat to make the urine acid and anti-bacterial do not remain ketotic for more than a few weeks. This has not yet been satisfactorily explained, but there is evidence that in subjects suffering from obesity, successive periods of starvation cause ketosis in a diminishing degree (Folin and Denis), a fact which suggests that the body can become more and more capable of using fat.

Enzymes in Fat Metabolism.—Esterases, since they hydrolyse esters and are present in many tissues, probably play a part in assisting in hydrolysis and synthesis of fat; the reaction which they bring about being reversible and the requirement of the body determining the direction.

The Essential Fatty Acids.—Some fatty acids, linoleic, linolenic, and arachidonic, are necessary for the proper growth and skin health of rats, but no clear-cut cases of the deficiency in man have been described.

Protein Metabolism.

In discussing the metabolism of carbohydrates and fats in the animal organism, it has been shown that the changes suffered by these components of the diet are essentially related to the production of mechanical energy, or heat. Protein may in part similarly be used as fuel, but its most important function is growth and repair. Protein alone among the foodstuffs contains the elements essential for the construction of new tissue, not only in the growing animal but also in the adult, where tissue wastage is constantly occurring owing to wear and tear processes. Moreover, it is becoming evident that these same elements are also required for the elaboration of substances of importance in the regulation of the organism, *e.g.* thyroxine. Hence it is seen that the protein of the food plays a rôle in the animal organism which cannot be undertaken by any of the other constituents of the diet.

Destination of the Amino-Acids.—Concerning the actual mode of this elaboration of new tissue and of regulative secretions very little is known. Nevertheless, available evidence indicates that the amino-acids, which we have seen are the ultimate breakdown products of the protein of the food during digestion in the alimentary canal, are intimately connected with this process. Van Slyke, for example, investigating the fate of amino-acids intravenously injected, found that not only did they rapidly disappear from the blood-stream, but also that this disappearance was due to their absorption by the tissues.

The increase of amino-acids after the injection was greatest in the liver, though the kidney and muscles appeared to retain their quota for a longer time. The fall in the liver amino-acids which takes place after the first hour was, moreover, accompanied by a rise in the blood urea and, as will be seen later, these two phenomena are closely related. It is thought that normal absorption of amino-acids by the tissues takes place in much the same way. Having thus loaded themselves with amino-acids, the tissues proceed to pick out those they particularly require, either to incorporate them into their own substance, or for the production of secretions; those amino-acids not so required, however, may be retained or transferred by way of the blood-stream to the liver, where they are broken down and the non-amino part used as fuel. There are, then, two main processes in protein metabolism; firstly, the building up of amino-acids from the blood-stream into the tissues and special substances like the hormones and bile acids, and secondly, the breaking down of the amino-acids not so required.

In addition to the metabolism of the protein of the diet, one must also remember that amino-acids are liberated from body

protein during tissue wastage and that every living tissue is periodically replaced. These amino-acids are dealt with in exactly the same way as those of the diet, but as would be expected such protein metabolism does not vary in amount like that of the diet.

Folin has classified protein metabolism on this basis. Metabolism which is closely related to the synthesis and breakdown of body tissue is called **endogenous**, while that not so related is called **exogenous**.

The products of exogenous metabolism in the urine are those which vary with the diet. Those of endogenous metabolism are unaltered by a diet rich or poor in protein, since they depend on the constant breakdown of the tissues of the body and are creatinine, neutral sulphur, and a small quantity of urea and uric acid. In conditions of excessive tissue breakdown, *e.g.* during involution of the uterus and in fever, the creatinine is much increased. It should be noted that the products of endogenous metabolism go directly to the kidney without passing to the liver. Ingested neutral sulphur, *e.g.* cystine, becomes oxidised to inorganic sulphur in that organ.

In the liver, as we have said, the amino-acids are **deaminated**, that is, they lose their NH_2 groups. Dudley and Dakin have suggested that this is probably the result of simple dissociation in which the acid is broken down to ammonia and aldehydes, a reaction possibly accelerated by enzymes but certainly not requiring much oxygen.

The process of deamination is the first in the **formation of urea**. The subsequent stages have been the subject of a considerable amount of research.

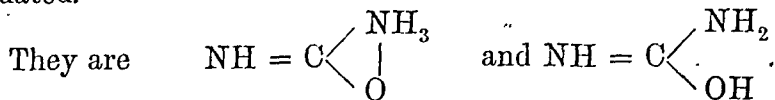
It was shown, for example, by Schröder in 1882 that ammonium carbonate, $\text{O} = \text{C} \begin{matrix} \text{ONH}_4 \\ \text{ONH}_4 \end{matrix}$ if perfused through the liver, was con-

verted into urea, and it has therefore been considered that this substance is probably an intermediate stage in the formation of urea normally. The feeding of ammonium carbonate to animals also causes an increase in the excretion of urea. This does not prove, as was first thought, that ammonium carbonate is a necessary precursor of urea but only that it can be a source of CO_2 and NH_3 for its formation.

Because of this it used to be considered that the formula of urea was $\text{O} = \text{C} \begin{matrix} \text{NH}_2 \\ \text{NH}_2 \end{matrix}$, but Werner has pointed out that urea

forms only one salt with nitric acid and not two, which would be the case if there were two basic (NH_2) groups in the molecule, and

has suggested formulæ in which the two nitrogens are differently situated.



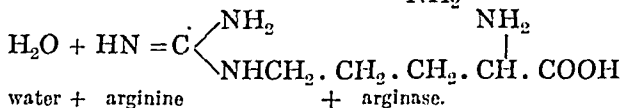
These formulæ do not satisfy many biochemists, and especially physical chemists, who find that the reactions of urea are not consistent with it.

Actually Bell, Gillespie, and Taylor have pointed out that the objection of Werner is unjustifiable because urea is such a weak base that the two salts could not really be expected. They point out that a similar state of affairs occurs in the case of the weak acid H_2CO_3 which forms one salt NaHCO_3 easily, but Na_2CO_3 only with difficulty and only in very alkaline solutions. They have calculated that similarly the acidity necessary to make the second salt from urea with nitric acid is beyond that of pure nitric acid.

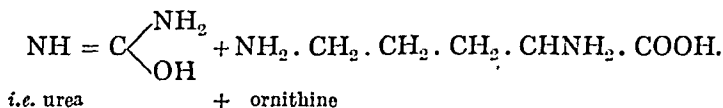
It has also now become known that urea is formed if slices of liver are supplied with ammonia and carbonic acid, and that this reaction is greatly accelerated by the presence of the diamino-acid ornithine.

Krebs has therefore suggested that the formation of urea is as follows, although it is not certain that all urea is formed in this way. The ammonia and carbon dioxide combine with ornithine to form arginine. In the liver a powerful enzyme, arginase, is present which breaks down arginine to urea and ornithine, which can be used over again. This is indicated by the following formulæ, in which it is seen that arginine contains in the α position the usual NH_2 group and at the other

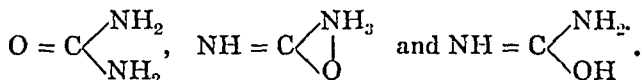
end of the chain a guanidine group, $\text{NH} = \text{C} \begin{array}{c} \text{NH}_2 \\ | \\ \text{NH}_2 \end{array}$ which is very like urea.



This gives



It seems likely that in the first stage the arginine is not formed directly but through an intermediate product, citrulline, which is formed by the action of ornithine on the ammonia and carbon dioxide and which is then converted into arginine by further ammonia. We have thus three possible formulæ for urea :



The whole subject of the exact steps by which urea is formed and its formula are by no means settled. It appears more than likely that it cannot be represented by any single static formula.

The whole point of this elaborate arrangement is to produce from the alkali ammonia a soluble neutral substance, urea, which

can be easily eliminated or from which, as we shall see, ammonia is very readily available when it is necessary to neutralise acid products in the blood. This neutralisation takes place in the kidney. (See Ammonia in the Urine.)

The process of urea formation takes place in the liver, and if an Eck fistula is made (*i.e.*, the portal vein is joined to the vena cava) so that the liver is short-circuited, no urea is formed. Mann and Magath have shown that removal of the liver causes a steady decrease of the urea in the blood and urine, provided urine secretion

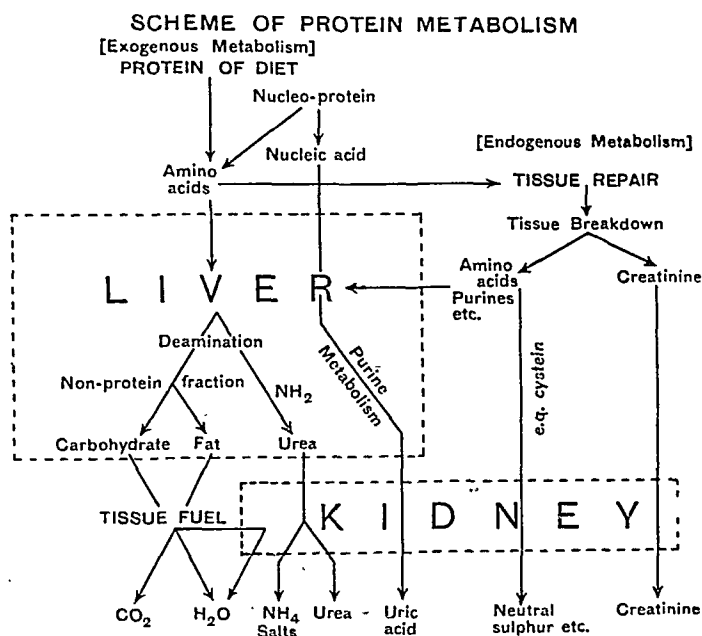


FIG. 170.

continues. If the flow of urine ceases or the kidneys are removed, the blood urea remains constant, indicating that urea is not destroyed in the body. The liver is, however, not the only site of deamination, indeed deaminising enzymes are found in many tissues. Older experiments with the Eck fistula showed an accumulation of ammonia in the blood and indicated that deamination might take place in other tissues. It has now been shown that the δ -amino-acids are deaminised in the kidney. It has also been found that ammonia is formed by an asphyxiated heart-lung preparation.

The urea formed in the liver passes into the blood-stream and thence by way of the kidney into the urine.

The reverse process, of making ammonia from urea, also takes place in the kidney. This is dealt with further in relation to the ammonia of the urine.

The Fate of the Non-Amino Fraction.—What remains of the amino-acids after deamination is oxidised to ketonic acids and some

subsequently to hydroxy-acids, such as lactic acid, for final oxidation. Some, such as alanine or glycine, may be converted through glucose into fat or oxidised according to the requirements of the body; others, like leucine and tyrosine, may yield acetone bodies.

In certain circumstances such as in diabetes or starvation, protein may become an important source of carbohydrate and body fuel.

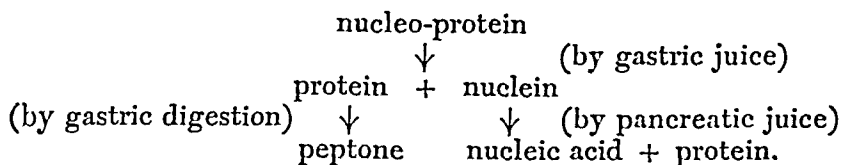
Other products of protein metabolism are excreted in the urine. Of these the sulphates are the most important, and since almost all proteins contain the sulphur containing amino-acids such as cystine the sulphates in the urine may, like the nitrogen excreted, be taken as an indication of the amount of protein metabolism. (See Lewis, 1924.)

The various destinations of protein are indicated conveniently in the above schema.

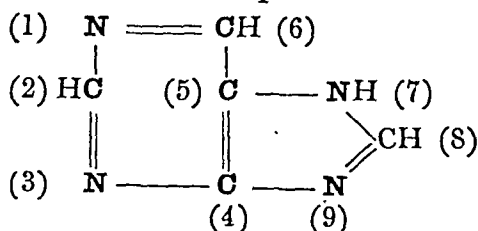
Purine Metabolism.

We have yet to consider the metabolism of the special group of proteins called nucleo-proteins. As the name suggests, these compounds contain nucleic acid, a complex organic acid containing phosphorus, which is found widely distributed in animal and vegetable tissues. It is an important constituent of nuclei and is, therefore, present in quantity in cellular organs such as the liver, thymus, pancreas, lymphatic glands, and testes. Moreover, in man, it is the precursor of uric acid, and a study of its metabolism is therefore of importance.

During digestion the nucleo-proteins undergo a variety of changes which primarily break them up thus:—

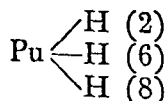


The nucleic acid is split into constituent nucleotides by the nuclease of the intestinal juice and wall, the final end-products which pass into the blood are amino-acids, from the protein part, and purines, pyrimidines, phosphoric acid, and hexose (or pentose), from the nucleic acid. The constitution of purine is



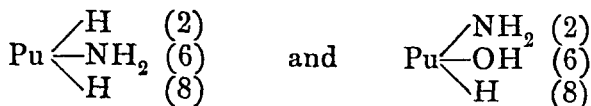
The purine ring is shown in dark letters.

or more simply

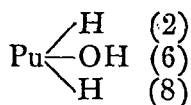


where Pu represents the purine ring and the numbers indicate the position of the substituting groups.

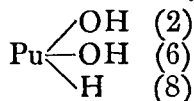
The more important purines (nucleotides) from our point of view are adenine and guanine, whose simpler formulæ are respectively



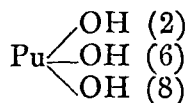
These two compounds, after absorption from the intestine, pass to the liver and other tissues, where they are deaminised in much the same manner as amino-acids, by the respective *deaminases* adenase and guanase. Adenine, under these conditions, yields hypoxanthine, or 6-oxy-purine



while guanine yields xanthine or 2, 6-dioxy-purine



Hypoxanthine and xanthine are then oxidised with the formation of *uric acid*, 2, 6, 8-trioxy-purine,

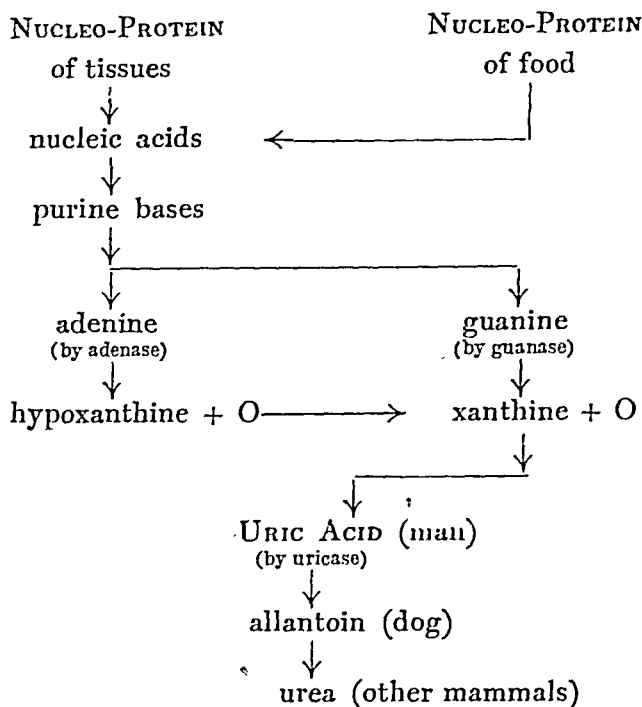


which is excreted in the urine as sodium and potassium salts.

While the changes thus described are taking place in the liver, the nucleic acid, which is a constituent of all cells, also suffers similar changes. Hence the uric acid, which finally appears in the urine, is partly endogenous in character, and partly exogenous.

While in man the uric acid so formed is excreted as such, yet many mammals, particularly the dog, are able to carry the process of oxidation one stage further, with the result that one of the purine rings is broken and allantoin is formed. In the urine of these animals allantoin thus largely replaces uric acid. In other mammals again, the allantoin so formed appears to be broken up with the ultimate formation of urea.

For our present purpose we might summarise the above changes simply, thus:—



The mode of excretion of uric acid in man is dealt with under "Urine."

It is of interest that the chief nitrogenous constituent of birds' urine is uric acid, and here the uric acid appears to be built up in the liver from the urea produced during the ordinary processes of protein metabolism. That such a synthesis takes place in the bird can be shown by cutting out the liver from the circulation. Under these conditions it is found that ammonium lactate accumulates in its blood. (Jones, 1920; Rose, 1923; also Levine and Base, 1931.)

The function of nucleic acids and their derivatives is becoming a subject of increasing importance, and is discussed by Drury, 1936. Some of these, such as adenosine triphosphate, are intense vasodilators as shown by Fleisch. There seems little doubt that the substances contained in nuclei are of the greatest importance in controlling the activity of cells. (See Needham, 1925.)

The Essential Amino-Acids and Protein Synthesis.

The study of protein digestion and subsequent metabolism indicates how the organism can construct the proteins peculiar to itself and maintain its chemical individuality, although the proteins

taken vary so widely in composition, especially in regard to their amino-acid content.

The evidence indicates that in the first instance the organism breaks down all foreign proteins into their constituent amino-acids and subsequently uses such amino-acids as it requires to build up its own protein.

In the making of animal proteins, however, ten **essential amino-acids** appear to be more important than others for certain animals. Some can be made apparently by the animal from simpler substances but others must be supplied, at least to carnivorous animals.

The ten essential amino-acids are:—

Arginine
Histidine
Isoleucine
Leucine
Lysine

Methionine
Phenylalanine
Threonine
Tryptophan
Valine,

and from these the other amino-acids may be made.

By feeding animals on diets deficient in different amino-acids it has been possible to obtain accurate information on the subject. This has been done especially by Hopkins, Osborne, Mendel, Rose, Sherman, and many others, and it is of interest to recall that it was such experiments also which led to the discovery of vitamins.

In the young animal the choice of diet is more important than in the old, which appears to have a greater power of synthesis as it has less power of growth.

In this connection then the amino-acid content of proteins is of the utmost importance. Some proteins such as gelatine contain no tyrosine or tryptophan. Zein, the protein of maize, contains no tryptophan, lysine, or glycine. Casein, the protein of milk, contains no glycine and little cystine. Gliadin, the protein of wheat, has no glycine or phosphorus. Purines are absent from caseinogen, gliadin and edestin.

Young rats thrived on all these proteins, but a puppy would not thrive on gliadin as its only source of nitrogen, although its mother thrived excellently and was able to produce and nurture her young normally.

By such experiments, it has been found that lysine, histidine, and arginine are essential for growth, but growth takes place more rapidly if cystine is present also in the diet. Tryptophan is essential for life and for the maintenance of body-weight, while tyrosine is very important, probably because some of the substances (such as the hormones, adrenaline and thyroxine) which control many bodily activities are derived from it. Tyrosine may, however,

be absent if tryptophan or some of the other aromatic amino-acids, especially phenylalanine, are present. It has become apparent that an amino-acid essential for growth is not necessarily essential for maintenance. Glycine is, however, not essential as it can be easily synthesised by the organism. Lysine can be made by adults but not by the young, at least in adequate amounts for growth. A deficiency in arginine can be compensated for by giving extra histidine, but not the reverse. Similarly, cystine can be dispensed with if methionine is present. It is claimed that α -amino- β -hydroxy-*n*-butyric acid is essential (Rose).

Many experiments have been made to try to get animals and moulds to take up abnormal amino-acids, but it has always been found that the protein of living organisms is constant in composition and independent of the food given.

The supply of essential amino-acids is specially important when tissue has to be built up, *e.g.* in the young, in pregnancy, lactation, and in recovery from wasting disease, or following a period of undernourishment.

A knowledge of amino-acids is then of the greatest importance in the construction of dietaries and it becomes evident that many articles of diet are more complete than others so far as amino-acids are concerned, depending on the amount of each they contain.

For growth, eggs and milk are specially valuable although the latter is deficient in iron. For general purposes the following is the order of merit—eggs, milk, meat, whole wheat, potato, oats, corn, white flour and beans. The reader should at this stage consult the table given earlier in relation to the constitution of proteins.

Special Protein Metabolism.—In addition to the processes described above, which concern the nitrogen of the protein molecule, the body has certain special mechanisms to deal with any other elements in proteins such as sulphur or phosphorus. The method of excretion of the surplus intake of such elements is dealt with in the chapter on Urine.

It is the necessity for the essential amino acids which probably explains why the normal animal takes in amounts of protein so greatly in excess of what is needed to maintain its nitrogen loss (see below).

Protein Storage.—There is no evidence that the body stores protein in the sense that it may store carbohydrates or fat to an almost unlimited extent. There is, however, evidence that there are stores of protein for special purposes, for after hæmorrhage it has been found that the blood proteins are rapidly made up, apparently from the liver, for this does not occur if the liver is removed, and food does not appear to be essential. (Beattie, 1943.)

Starvation.

The term "starvation" is used very loosely. In a scientific sense it may be taken to include any deficiency in the food or water intake, but by convention it is understood as meaning complete deprivation of food, water only being supplied. In man it is possible to study the subject in some detail, since after the first three or four days the desire for food disappears although the subject becomes weak.

During starvation the body gradually loses weight; the basal metabolism and temperature, after a preliminary rise, fall; the functions get weaker by degrees, and ultimately death ensues when the body has lost about 50 per cent. of its original weight. Death may be delayed somewhat by artificial warmth, so that the strain on the internal production of heat is not so great. If water is given, life may continue for rather more than a month. The age of the animal influences the time at which death occurs. This statement was originally made by Hippocrates, and has been borne out by the experiments of Martigny and Chossat. Young animals lose weight more quickly, and die after a smaller loss of weight than old.

At first (one to three days) stores of carbohydrate, especially the liver glycogen, are burnt, but this store is limited and the body uses it sparingly. The muscles do not lose their glycogen appreciably and the heart not at all. Subsequently fat becomes the chief source of energy as is seen by the fall in the respiratory quotient almost to 0.7. As might be expected, the combustion of fat is incomplete and acid products are excreted in the urine.

The blood sugar also falls, but later, for some unexplained reason, it rises again, possibly because of the conversion of fat into carbohydrate. It should be noted that the fat which is used is that of the fat depôts and not the fat which is a part of the structure of practically all cells.

The utilisation of protein is seen in the nitrogen excretion in the urine.

The excretion of nitrogen falls quickly at the commencement of starvation, and even on the first day sinks to half the normal, like that of a subject on a low protein diet. This lessening goes on for a few days, after which it remains constant; about the end of the fourth week it rises again when the fat of the animal has been used up, and the body makes an increased call on the protein constituents of its protoplasm—"the premortal rise." With the onset of symptoms of approaching death, which is sometimes accompanied by convulsions, the excretion of nitrogen rapidly falls again, probably owing to renal failure.

The metabolic rate falls, but it is important to note that wasting

does not occur to an equal extent in all the tissues and organs. Those which are most essential to life are fed at the expense of the others; thus the heart loses little or none, and the central nervous system loses at most 3 per cent. of its weight. The fat nearly all disappears, at least 97 per cent. of it being used up; muscles lose 30 per cent. of their original weight, and most of the other organs suffer also but in varying degrees. Taking the total loss as 100, Voit gives the loss due to that of individual organs as follows:—

Bone	5.4	Pancreas	0.1	Brain and cord . . .	0.1
Muscle	42.2	Lungs	0.3	Skin and hair . . .	8.8
Liver	4.8	Heart	0.0	Fat	26.2
Kidneys	0.6	Testes	0.1	Blood	3.7
Spleen	0.6	Intestines	2.0	Other parts	5.0

The subject of fasting is well discussed by Graham Lusk, 1921, and by Morgulis, 1923.

The study of starvation is important, as it gives information regarding the so-called **nitrogen equilibrium**, or balance between nitrogen output and intake of the body. It is found that in carnivora, in order to make the nitrogen intake equal to that excreted, about three times the amount excreted in starvation has to be given, but in man nitrogen equilibrium can never be attained on protein alone. The more nitrogenous food given, the more is utilised, and the excretion always exceeds the intake. The additional protein is really used as fuel to supply the essential energy requirements and does not prevent tissue wastage. The fuel requirements are actually increased by the protein itself in virtue of its specific dynamic action (*q.v.*) on metabolism. The fuel can, indeed, be more adequately supplied by carbohydrates and fats, which may be looked upon, therefore, as **protein-sparers**, and, if these are given, nitrogen equilibrium is possible in man and is more readily produced in carnivora than in their absence. Carbohydrates are better protein-sparers than fats, since they are more readily oxidised. They will therefore reduce tissue wastage in starvation. It is suggested that the protein-sparers make it possible for the products of tissue breakdown to be used over again, and the importance of carbohydrate in the diet during repair is emphasised. In emergencies a remarkable interconversion of the major foodstuffs can occur. (See Rapport, 1930.)

The Biological Value of Proteins.—When we take in protein we do so essentially to replace tissue wastage, and there is, therefore, a certain *irreducible protein minimum* below which the protein intake cannot be reduced without affecting the nitrogenous equilibrium. It has been found that certain sources of protein, *e.g.*

meat, eggs and milk, have a much greater value than others, as is shown by the fact that less of their protein is required to maintain nitrogenous equilibrium than of vegetable. These substances are said, therefore, to have the highest biological value, and it will be noticed that they are of animal origin. It is probable that this value depends on the amino-acids which they contain; and the vitamins commonly associated with them. We have already noted that in the construction of dietaries such articles are designated as "first-class" proteins since they maintain young animals at a maximum rate of growth.

CHAPTER XXXV

THE LIVER

THE **Liver**, the largest gland in the body, is an extremely vascular organ, and receives its supply of blood from two sources, viz., from the *portal vein* and from the *hepatic artery*, while the blood is returned from it into the inferior vena cava by the *hepatic veins*.

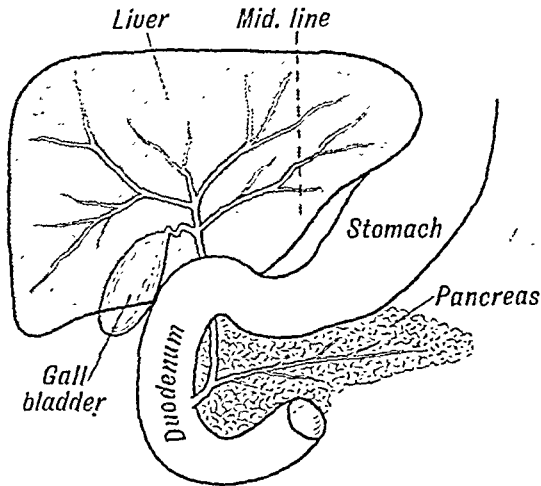


FIG. 171.—Diagram of the liver with the gall-bladder below it.

Its secretion, the *bile*, is conveyed from it by the *hepatic duct*, either directly into the intestine, or, when digestion is not going on, into the *cystic duct*, and thence into the gall-bladder, where it accumulates until required.

The liver is in origin a tubular gland, but as development progresses it soon loses all resemblance to the tubular glands found elsewhere. It is made up of small roundish or oval portions called *lobules*, each of which is about $\frac{1}{16}$ of an inch (rather more than 1 mm.) in diameter, and composed of the liver cells, between which the blood-vessels and bile-vessels ramify. The *hepatic cells*, which form the glandular or secreting part of the liver, are of a spheroidal form, but are rendered polygonal from mutual pressure. Each possesses a nucleus, sometimes two. The cell protoplasm contains numerous fatty particles, as well as a variable amount of glycogen.

The portal vein (PV), hepatic artery (HA), and hepatic duct (BD) run in company (fig. 172). Running together through the substance of the liver, they are contained in small channels called *portal canals*, their immediate investment being a sheath of areolar tissue continuous with Glisson's capsule which coats the liver.

In its course through the liver the portal vein gives off small branches which divide and subdivide *between* the lobules surrounding

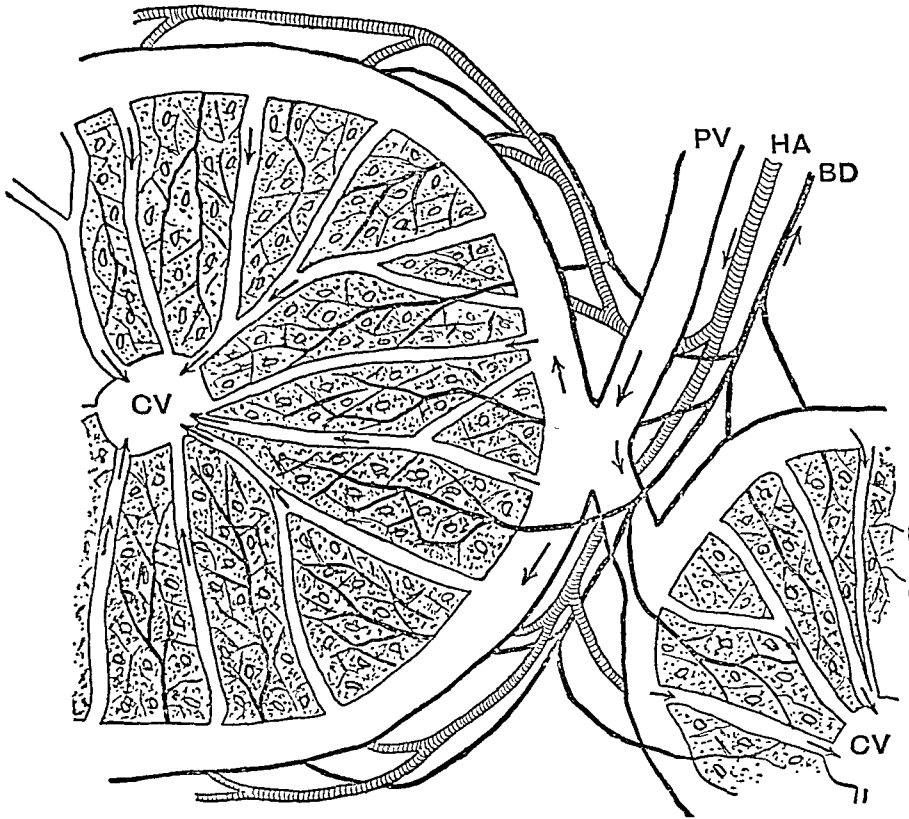


FIG. 172.—Diagram to show the main structures of the liver. For clearness the cells and capillaries of the liver have been drawn unduly large and the smaller vessels omitted.
(Modified from Burton-Opitz.)

them and limiting them, and from this circumstance are called *inter-lobular* veins. From these vessels a dense capillary network is prolonged into the substance of the lobule, and this network converges to a single small vein, occupying the centre of the lobule (CV in fig. 172), and hence called *intra-lobular*.

The *intra-lobular* veins discharge their contents into veins called *sub-lobular*; these, by their union, form the main tributaries of the *hepatic* veins, which leave the posterior border of the liver to end by two or three principal trunks in the inferior vena cava, just before its passage through the diaphragm.

The endothelial lining of the liver capillaries appears to be in many places incomplete, and its cells are irregularly branched and more or less isolated from their neighbours. They are called the *stellate cells of Kupffer*. More detailed study and special stains indicate that the endothelial lining is really continuous (Berry and Gilding) and that the blood does not come into direct contact with the liver cells as once thought.

The hepatic artery, the chief function of which is to distribute blood for nutrition to Glisson's capsule, the walls of the ducts and blood-vessels, and other parts of the liver, is distributed in a very similar manner to the portal vein, its blood being returned by small branches which pass into the capillary plexus of the lobules which connects the *inter-* and *intra-*lobular veins.

The bile-duct divides and subdivides in a manner like the portal vein, the larger branches being lined by *columnar*, and the smaller by small *polygonal* celled epithelium.

The bile capillaries commence between the hepatic cells; they are always bounded by hepatic cells on all sides, and are thus separated from the nearest blood-vessel by at least the breadth of one cell. The bile capillary corresponds to the lumen of a test-tube composed of cells, vessels being on the outside.

The *inter-cellular* network of bile capillaries may be shown (Chrzonszewsky) by injecting intravenously a saturated aqueous solution of sulph-indigotatate of soda. The animals are killed an hour and a half afterwards, and the blood-vessels, washed free from blood, are injected with gelatin stained with carmine. The bile-ducts are then seen filled with blue, and the blood-vessels with red material. If the animals are killed sooner than this, the indigo pigment is found within the hepatic cells, thus showing that it is through their agency that the canals are filled.

Pflüger and Kupffer later discovered that the relation between the hepatic cells and the bile canaliculi is even more intimate, for they demonstrated the existence of vacuoles in the cells communicating by minute *intra-cellular* channels with the adjoining bile canaliculi.

Intra-cellular canaliculi in the liver-cells are not unique. Recent research by Golgi's method has shown that in the salivary and gastric glands, and in the pancreas, there is a similar condition.

Schafer has further demonstrated that the liver-cells contain not only the intracellular bile canaliculi, but also intracellular blood canaliculi passing into the cells from the capillaries (sinusoids) between them. These are too minute to admit blood-corpuscles. The liver-cells take certain materials from the plasma and elaborate the constituents of the bile, the bile salts, and the bile pigments. These substances are in part formed by the hepatic cells, and in part are modified by the liver after having been manufactured elsewhere, *e.g.* bile pigments (see

Blood). We thus see that in the liver, lymph does not act as an intermediary as it does in the formation of other secretions.

The functions of the liver have of recent years been greatly elucidated by the work of Mann and Magath, who have successfully removed the organ in dogs by first causing to be established a collateral circulation through the azygos and internal mammary veins. Since the relation of the liver to metabolism is dealt with under Intermediate Metabolism, the main facts, together with the effects of extirpation, need only be summarised.

The Functions of the Liver.—The liver, as we have seen, plays an important part in the intermediate metabolism of carbohydrate, fat, and protein.

Carbohydrate Metabolism.—The storage of glycogen and mobilisation of glucose (pp. 480 *et seq.*). The conversion of fructose and galactose into glucose. In starvation the formation of glucose from protein.

Removal of the liver causes a marked hypoglycæmia, producing general loss of all functions, and death ensues in two hours. If, however, glucose is administered the animal makes a remarkable recovery and survives for twenty-four hours. These results occur even after the glycogen of the liver has been removed by previous starvation, thus showing that it has been in such circumstances concerned in the formation of glucose probably from protein. (See Mann and Magath, 1927.)

Fat Metabolism.—The desaturation of fats prior to oxidation (p. 488).

Protein Metabolism.—Deamination of amino-acids, formation of urea and uric acid (see Protein Metabolism and Purine Metabolism).

Bile Formation.—Removal of liver, like obstruction of its ducts, causes the accumulation of bile pigment in the blood as the pigment which is the product of the breakdown of red blood-corpuscles is no longer excreted (see The Fate of Red Blood-Corpuscles).

Detoxicating Function.—The liver plays an important part in dealing with poisonous substances, *e.g.* drugs, absorbed from the alimentary canal. This function of the liver is dealt with at the end of this chapter.

Blood Formation.—The liver is concerned with the formation of both the plasma and corpuscles of the blood. It apparently acts as a storehouse of the blood-forming factor which is formed from the interaction of intrinsic factor of the gastric juice and the food. Extracts of liver are therefore extensively used in the treatment of pernicious anæmia in which the formation of red blood-corpuscles is defective. The liver stores the iron from effete corpuscles.

The liver also forms fibrinogen, the clotting protein of the blood, and acts as a storehouse of it which can be called upon in hæmorrhage. For this function vitamin K is necessary.

Heparin, the substance which in minute amounts will prevent the blood from clotting may, as its name suggests, be extracted from the liver. It is apparently produced by the mast-cells of the connective tissue.

Admittedly it is a little difficult, even allowing for diversity of cells, to see how the liver can perform so many different functions, and it seems probable that it may act in some fundamental way in relation to several processes. It has been shown, too, by the injection of dyes, that the various streams of blood do not necessarily mix in the liver. The blood from the spleen, for example, goes to the middle lobe.

Bile.

Bile is secreted by the liver, stored in the gall-bladder and is poured into the duodenum. It may be collected from the bile-duct or in man by means of a tube which is swallowed into the stomach and which passes into the duodenum if the subject lies on his right side. Under suitable conditions (see below) the bile drips out freely. It is stated that 500 to 1000 c.c. may be excreted daily.

Bile is being continuously poured into the intestine, but there is an increased discharge from time to time (see below).

The Constituents of the Bile are the bile salts proper (taurocholate and glycocholate of sodium), the bile pigments (bilirubin, biliverdin), a mucinoid substance, small quantities of fats, soaps, cholesterol, lecithin, and mineral salts, of which the carbonates and phosphates of calcium are the most important.

Bile is a yellowish, reddish-brown, or green fluid, according to the relative preponderance of its two chief pigments. It has a musk-like odour, a bitter-sweet taste, and an alkaline reaction.

The specific gravity of human bile from the gall-bladder is 1026 to 1032; that from the duct, 1010 to 1011. The solids increase from 2.0 to 11 per cent. from absorption of water and addition of mucus.

The Bile Salts.—The human bile contains the sodium salts of complex amino-acids called the bile acids. The one, *glycocholic acid* ($C_{26}H_{43}NO_6$), is derived from the amino-acid glycine and cholic acid, whose origin is uncertain (it is thought to be derived from cholesterol or to have a similar origin); the other, *taurocholic acid* ($C_{26}H_{45}NO_7S$), is derived from cholic acid and taurine, a sulphur-containing amino-acid formed from cystine. The bile acids are hydrolysed by dilute acids and alkalis into their components. The constitution of the bile of different animals varies considerably. In human bile several cholic acids which are hydroxy derivatives of cholanic acid are found. Of these desoxycholic acid is most important as it forms choleic acids with many substances especially fatty acids, sterols and phenols which are soluble and diffusible in acid solution.

Otherwise these substances would be insoluble in acid. In man glycocholic acid predominates. Chemically the bile acids are very closely related to and have a similar structure to cholesterol. High protein diet or administration of cholic acid increases the excretion of bile salts, while fasting or the ingestion of sugar lowers it.

The colour reaction called **Pettenkofer's reaction** is due to the presence of cholic acid. Small quantities of sucrose and strong sulphuric acid are added to the bile. The sulphuric acid acting on sugar forms a small quantity of a substance called *furfuraldehyde*, in addition to other products. The furfuraldehyde gives a brilliant purple colour with cholic acid.

The Bile Pigments.—These are iron-free derivatives of hæmoglobin; the body retains the iron for other uses. The two chief bile pigments are bilirubin and biliverdin. Bile which contains chiefly the former (such as dog's bile) is of a golden or orange-yellow colour, while the bile of many herbivora, which contains chiefly biliverdin, is either green or bluish-green.

Bilirubin has the formula $C_{33}H_{36}N_4O_6$: it is thus an iron-free derivative of hæmoglobin. The iron is apparently stored up in the liver-cells, perhaps for future use in the manufacture of new hæmoglobin. Bile contains only a trace of iron; bilirubin is isomeric with hæmatoporphyrin.

Biliverdin ($C_{33}H_{36}N_4O_8$) may occur as such in bile; it may be formed by simply exposing red bile to the oxidising action of the atmosphere; or it may be formed as in Gmelin's test (see Urine) by the more vigorous oxidation produced by fuming nitric acid.

Hydrobilirubin ($C_{32}H_{44}N_4O_7$).—If a solution of bilirubin or biliverdin in dilute alkali is treated with sodium amalgam or allowed to putrefy, a brownish pigment, which is a reduction product, is formed called hydrobilirubin. It shows a dark absorption band between *b* and F, and a fainter band in the region of the D line.

This substance is interesting because a similar substance is formed from the bile pigment by reduction processes in the intestine, and constitutes *stercobilin*, the pigment of the fæces. Some of this is absorbed and ultimately leaves the body in the urine as one of its pigments called *urobilin*. A small quantity of urobilin is sometimes found preformed in the bile.

The Origin of Bile Pigment.—We have seen (p. 361) that the bile pigments are formed from residues of broken-down red blood-corpuscles, by the reticulo-endothelial system. The bilirubin is modified by the liver, as is indicated by the van den Bergh reaction.

The test solutions are—

(A) Sulphanilic Acid	1 gram
HCl (conc.)	15 c.c.
Distilled Water	1000 c.c.
(B) Sodium Nitrite	0.5 per cent. solution

Immediately before use *A* and *B* are mixed in the proportion of 100 to 3 respectively.

If added to bile the direct reaction (bluish-violet) is obtained, but if to normal blood serum no colour appears until 96 per cent. alcohol has been added, *i.e.* the indirect reaction (violet-red). The modification, which is obscure, is due to the liver, but the reaction has been of great value in detecting and estimating the presence and amount of modified and unmodified bile pigment in the blood. In simple obstruction of the bile passages the pigment which has been modified passes back into the blood-stream the serum of which then gives the direct reaction. The presence of an excessive amount of bile pigment in the blood causes the mucous membranes, the white of the eye, and the skin to appear yellow. This is known as Jaundice. Its depth is measured by the *Icterus Index*—see p. 511.

Cholesterol.—Small quantities of this substance are excreted in normal bile. Gall-stones commonly consist of precipitated cholesterol, to which may be added bile pigments and calcium carbonate.

The Secretion of Bile.—This takes place during the day, rather than during the night when glycogen is being stored. The cells concerned are the more central cells of the lobule, but, as shown histologically, the other cells become active if more bile is needed. The bile is secreted at a much lower pressure than are the secretions of the salivary glands, but this is to be expected from the fact that in the latter case the pressure of the blood in the main vessel supplying the gland is arterial and not venous. Like other secretions, however, it is produced at a pressure higher than the blood supply.

The nervous mechanism is unknown, but it appears that bile is secreted under the influence of the action of secretin, which thus stimulates the liver as well as the pancreas, and through the action of the bile salts which are themselves reabsorbed from the intestine.

Schiff was the first to demonstrate this **circulation of the bile**, which relates chiefly, if not entirely, to the bile salts; by causing bile to be added to the diet of animals or led back to the duodenum from a fistula, the percentage of solids in the bile excreted is at once raised. The secretion of bile is increased by a variety of substances other than bile salts; of these the most important are tissue extracts generally. Meat increases the taurocholic acid and fat the cholesterol.

This circulation of the bile may be lost if the bile duct is brought to the surface for drainage purposes. Patients so treated and experimental animals slowly become very anæmic from the loss of the blood-forming factor; indeed it was this fact which led to the discovery that the liver contained such a factor (see Origin of Red Blood-Corpuscles).

The Storage and Excretion of Bile.—Bile is secreted particularly during the digestion of food, but when the stomach is empty it accumulates in the gall-bladder. During its stay in the gall-bladder the bile is concentrated and has mucus added to it (see Constituents of Bile). In starvation the bile-pressure may reach 300 mm. (of bile). This it does in virtue of the pressure at which it is secreted and because the sphincter, at the opening of the common bile-duct into the duodenum, is closed while the gall-bladder is relaxed. The resistance of the sphincter is therefore considerable (McMaster and Elman).

This sphincter, which is commonly called the sphincter of Oddi, has been variously described, but the work of Kirk and Gordon Taylor shows that in man it is not a circle of muscular fibres at the opening as its name suggests. Rather it is composed of fibres running longitudinally or obliquely which are prolonged into the villous processes with which the terminal segment of the duct abounds. The structure suggests that the opening is closed by a retraction of the papilla and an erection or pulling up of the villous processes, the whole arrangement being strengthened by the oblique passage of the duct through the duodenal wall.

When food passes through the pylorus the peristaltic waves pass over the duodenum, the sphincter at the opening of the bile-duct relaxes, and the gall-bladder and large ducts contract, driving out the accumulated bile. This mechanism appears to be under the antagonistic influences of the vagus and sympathetic, the former being motor. In cases of obstruction of the bile-duct by a gall-stone, excessive action of the plain muscle of these parts attempting to drive down the stone causes the intense pain of biliary colic from stretching the wall of the duct.

It is apparently the products of fat digestion which are concerned in this mechanism, as contraction is not complete until some time after the food enters the duodenum.

Ivy and his co-workers have discovered in the wall of the duodenum a substance like secretin which may be extracted and which brings about contraction of the gall-bladder if injected into the blood. This substance they call **cholecystokinin**.

Most purgatives, *e.g.* calomel and magnesium sulphate, stimulate the bile-expelling mechanism, and consequently the faeces becomes dark from the presence of bile pigment less altered than stercobilin. When it is desired to obtain samples of bile through the duodenal tube, a meal of cream and egg-yolk is given to cause the gall-bladder to contract. Evidence seems to favour the view that this rapid evacuation is due to a rapid rise in the pressure in the gall-bladder from a contraction initiated by cholecystokinin and reflex stimuli from the gut. At the same time as the gall-bladder contracts the sphincter of Lütken at its neck relaxes. The fact that the blood of a subject fed on egg-yolk causes the gall-bladder of

another to contract suggests that the egg causes the production of cholecystokinin. Meat and peptones cause excretion.

The patency of the bile passages may be studied by means of X-rays.

A dye, sodium tetra-iodophenolphthalein, opaque to X-rays, is eliminated in the bile after intravenous injection, and its excretion may be hastened by giving the patient a quantity of cream and egg-yolk. The X-ray shadow of the gall-bladder becomes more and more dense for some time after the period of maximum excretion of the dye, because of concentration of the opaque dye in the stored bile. Moreover, there is evidence that the gall-bladder absorbs some of the lipides of bile; this organ may therefore be of importance in regulating the amount of cholesterol leaving the body *via* the bile. The physiology of the gall-bladder is well discussed by Mann, 1924, and by Ivy, 1934.

The Functions of Bile.—Bile is alkaline; it therefore assists the pancreatic juice in neutralising the chyme that leaves the stomach. It assists the absorption of fats. It is also a solvent of fatty acids, of the fat-soluble vitamins or their precursors, *e.g.* carotene and ergosterol, and of cholesterol. The latter may be precipitated from solution by the products of bacterial growth and this gives rise to the formation of gall-stones.

Bile stimulates peristalsis in the *large* intestine and is used extensively for this purpose in enemata, especially after operations. The use of bile as a purgative was known to the ancient Egyptians.

When the bile meets the chyme the turbidity of the latter is increased owing to the precipitation of unpeptonised protein. This is an action due to the bile salts, and it has been surmised that this conversion of the chyme into a more viscid mass serves to hinder its progress through the intestines; it clings to the intestinal wall, thus allowing further digestion and absorption to take place.

It precipitates also pepsin and neutralises the hydrochloric acid of the stomach by regurgitating into the latter when it is empty.

Bile is readily putrescible but may diminish putrescence in the intestine by increasing absorption and lessening the amount of putrescible matter in the bowel.

Bile, as we have seen, acts as a stimulant to its own secretion.

Bile is also a means of excretion of cholesterol, iron, copper and calcium. Many drugs are also excreted in the bile, *e.g.* phenol.

Bile salts facilitate the absorption of vitamin K.

Removal of the Gall-Bladder.

The gall-bladder is liable to become the seat of chronic infection and very commonly gall-stones are precipitated. Removal of the organ is commonly practised with apparently no detriment (indeed

usually with benefit) to the patient. Some consider that the bile-ducts dilate to accommodate the bile, others consider that there is a continuous excretion of bile. The latter seems unlikely in view of the resistance of the sphincter. Some animals which secrete a more concentrated bile have no gall-bladder, *e.g.* the mouse and horse.

Tests for Liver Function.

Since, as we have seen, the liver converts lævulose into glucose, advantage is taken of this fact in determining liver function. If 100 grams of lævulose is taken none should appear in the urine, but this occurs if the liver is functionally upset by disease or large quantities of alcohol. The power of the liver to convert benzoic into hippuric acid (see below) may also be used as a test.

Icterus Index.

This is a convenient method of estimating the amount of bile in the blood. The colour of the plasma or serum is compared in a colorimeter with a standard 1-10,000 solution of potassium bichromate in distilled water. The colorimeter is set at 15 and

$\frac{15}{\text{Reading}} \times \text{dilution of serum}$ gives the index.

Detoxication in the Body.

From time to time poisonous substances are taken into the alimentary canal, intentionally or otherwise, and are absorbed into the blood-stream. Many common drugs are of this nature and would poison the subject if taken in sufficient amounts. In addition, toxic substances are produced especially in the alimentary canal as the result of bacterial action. The body gets rid of such substances in its excretions by the lungs (in the case of poisonous gases), by the intestine, and especially by the kidney. The substances may be excreted in an unchanged form, but more commonly they are changed in a variety of ways so as to render them harmless.

Oxidation.—Sometimes the oxidation is complete, as in the case of alcohol and other aliphatic compounds, but this cannot be completely done in the case of the aromatic compounds. Some of these are partly oxidised to benzoic or to phenylacetic acids. Indole, the product of putrefaction in the intestine, is oxidised to indoxyl and conjugation (see below) follows. In some cases the oxidation is the work of special enzymes such as those for the destruction of acetylcholine and adrenaline.

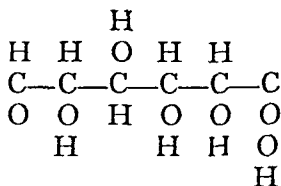
Reduction.—Typically this occurs when aromatic nitro-compounds are reduced to amino-compounds; thus picric acid,

$C_6H_2(NO_2)_3OH$, is converted into picramic acid, $C_6H_2(NO_2)_2(NH_2)OH$. The drug chloral, $CCl_3 \cdot CHO$, is reduced to $CCl_3 \cdot CH_2OH$ before being conjugated with glucuronic acid (see below).

Conjugation is brought about by several methods of which those by glycine, by glucuronic acid, and by sulphuric acid are the most important.

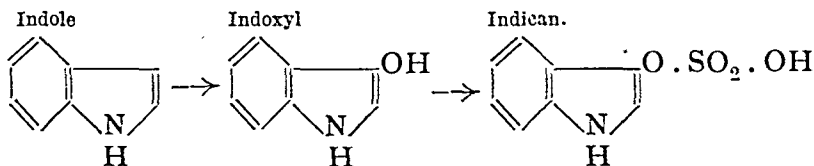
Detoxication by Glycine occurs in the case of many aromatic acids. This is seen typically when benzoic acid is converted into hippuric acid and is so common that hippuric acid is considered a normal constituent of the urine. Glycine for this purpose apparently may be made in the body, for if the diet is deficient in this respect the urea is reduced.

Detoxication by Glucuronic Acid is of special importance since the CHO -group of the glucuronates reduces copper salts and may be mistaken for sugar in the urine. The glucuronic acid probably originates from glucose but the process is not clear. Its salts are distinguished from glucose by their being lævorotatory and not being fermented by yeast. Its formula indicates that it is glucose with the end-chain (CH_2OH) -oxidised to $COOH$. It is



The glucuronate content of the urine is increased by several common drugs such as choral, chloroform, salicylates, camphor, morphine, antipyrine, phenacetin, turpentine, and saccharin.

Detoxication by Sulphuric Acid.—The formation of sulphuric esters or ethereal sulphates occurs in the detoxication of phenols absorbed from the large intestine (see p. 536). Indole which is also absorbed there is, as we have said, first oxidised to indoxyl and then converted into the ethereal sulphate *indican* which appears in the urine and is convertible into indigo blue. It is a measure of intestinal putrefaction. The reactions which occur are



Normal urine contains traces of such phenol compounds derived from the intestine.

Detoxication by Acetic Acid.—Amino-compounds such as *p*-amino-benzoic acid are detoxicated in this way.

Detoxication by Glutamine appears to be peculiar to man and the chimpanzee, man's nearest relative amongst the apes. It occurs in the detoxication of phenylacetic acid, but apparently not in that of its compounds.

Detoxication by Fixation.—In some cases the liver and other tissues appear to have the power of fixing substances in their tissues in an inert form. This occurs in the case of arsenic.

At present we know comparatively little about detoxication processes, but it is probable that most take place in the liver, and that they are of greater importance in relation to the resistance to infection than is generally supposed. It has been shown, for example, that *p*-amino-benzoic acid is required by the virulent organism the streptococcus and that the important sulphonamide drugs may act by making this substance less available to the bacteria.

CHAPTER XXXVI

THE URINARY APPARATUS

THE urinary apparatus consists of the kidneys, from each of which a tube called the *ureter* leads to the bladder, where the urine is temporarily stored; from the bladder a duct called the *urethra* leads to the exterior.

The **kidneys** are composed of a vast number of minute tubules the structure of which varies in its different parts, a fact which has an important bearing on its function in relation to the production of urine. Students who have not dissected the kidney should do so at this stage. Those sold for food are quite suitable for the purpose.

Each tubule begins in the cortex or outer zone of the organ as a dilatation, the *capsule of Bowman**; this encloses a tuft or glomerulus of capillaries, called a *Malpighian corpuscle*. The tubule leaves the capsule by a *neck*, and then becomes convoluted (*first convoluted tubule*), but soon after becomes nearly straight or slightly spiral (*spiral tubule*); then rapidly narrowing, it passes down into the medulla as the *descending tubule of Henle*; this turns round, forming a loop (*loop of Henle*), and passes up to the cortex again as the *ascending tubule of Henle*. It then becomes larger and irregularly zigzag (*zigzag tubule*) and again convoluted (*second convoluted tubule*). Eventually it narrows into a *junctional tubule*, which joins a straight or *collecting tubule*. This passes straight through the medulla, where it joins with others to form one of the *ducts of Bellini* that open at the apex of a pyramid into the pelvis of the kidney where the ureter commences. These parts are all shown in fig. 173.

In the *capsule*, the epithelium is reflected over the glomerulus. It is flattened like that lining a lymph space.

In the *neck*, the epithelium is still flattened, but in some animals, such as frogs, where the neck is longer, the epithelium is ciliated.

In the *first convoluted* and *spiral* tubules, it is thick, and the cells show a striated structure, except around the nucleus, where the protoplasm is granular. The cells interlock laterally and are difficult

* In his original paper Bowman says that this capsule was first described by Müller who did not then recognise its exact connections with the tubules.

to isolate. In the *narrow descending tubule of Henle* and in the *loop itself*, the cells are clear and flattened and surround considerable lumen; in the *ascending limb* they again become cuboidal striated

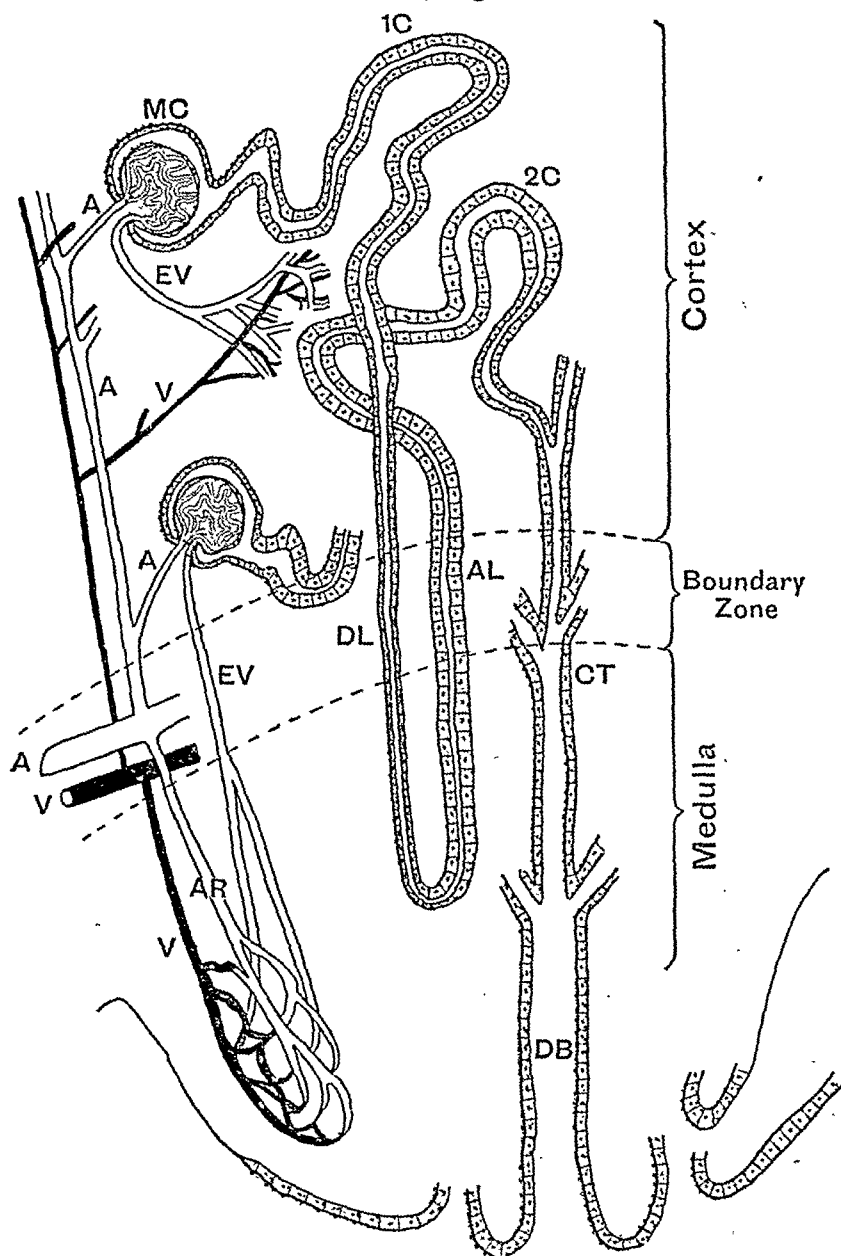


FIG. 173.—Diagram to indicate the general arrangement of the kidney. MC, Malpighian corpuscle; 1C, first convoluted tubule; 2C, second convoluted tubule; DL and AL, descending and ascending limbs of the loop of Henle; CT, collecting tubule; DB, duct of Bellini; A, artery; EV, efferent vessel; V, vein. (After Gray.)

and nearly fill the tubule. In the *zigzag* and *second convoluted* tubules the fibrillations become even more marked. The *junctional* tubule has a large lumen, and is lined by clear flattened cells

the *collecting* tubules and *ducts of Bellini* are lined by clear cubical or columnar cells.

The extent of the zone of clear cells in the loop of Henle varies a good deal in different animals.

The glomerulus with its tubule is known as a **nephron**, and it is calculated that there are a million such units in a kidney. Each nephron is 30-38 mm. in length.

The anatomical details of the vessels need not concern us here, but the important fact in relation to the function of the organ is that the arteries supply first the glomeruli and then the tubules (see fig. 174), which means that there are two sets of capillaries in the series and the blood-pressure in the second must obviously be much lower than that in the first. For convenience the vessels between the glomeruli and the tubules are known, not as veins, but as the *efferent vessels* of the glomeruli. The detailed structure of the tubule is given by Huber, 1909, and in different animals by Homer Smith.

The Function of the Kidney.

The function of the kidney is to separate the urinary constituents from the blood, and by this means the blood is maintained of constant composition. It is chiefly concerned with the excretion of water, chlorides, sulphates, and the products of protein metabolism. In these functions the kidneys co-operate with the skin. They also co-operate with the lungs in maintaining the normal acid-base equilibrium of the blood by varying the amount of carbon dioxide excreted. These inter-relationships are considered later.

We may sum up the process of urinary secretion as follows:—One fluid, the arterial blood, enters the kidney; two fluids, the venous blood and the urine, leave it. Both of these fluids are different in composition from the arterial blood. The following table gives the approximate values of the **principal constituents in the plasma of the arterial blood, and in the urine**. It must, however, be clearly understood that the various constituents may vary from time to time according to circumstances.

	Arterial Blood-plasma.	Urine.
	10 per cent.	4 per cent.
Total solids . . .	7.5 to 9	0
Proteins . . .	0.87	0.6
Chloride . . .	0.08	2.0
Urea . . .	0.10	0
Sugar . . .	0.003	0.05
Uric acid . . .	0	0.07
Hippuric acid . . .	0.001	0.1
Creatinine . . .	0.001	0.04
Ammonium salts . .		

How exactly the urine is separated from the blood and concentrated has been a subject of study and debate over a long period of years, but it is slowly becoming evident that although the kidney acts as a whole, its different parts act differently as their histological structure suggests. Thus it may be considered that the flattened epithelial cells of the glomeruli and possibly of the descending loops allow the passage of fluid by simple physical processes which are affected solely by the blood-pressure in the blood capillaries supplying them and the osmotic pressure of the blood constituents. A variation in this activity does not involve any alteration of the oxygen usage of the organ. The thicker cells of the majority of the tubules may be considered to have a more vital function, an increase in which requires the use of more oxygen.

A glance at the above table shows that while the urine as a whole is more dilute than the blood, certain constituents are present in greater concentration than they are in the blood. Moreover, it is evident that some substances have been concentrated to a greater extent than others. *Cf.* Creatinine and Urea.

It is convenient to consider the functions of the glomeruli and tubules separately.

The Function of the Glomeruli.

In the case of the glomeruli, the evidence is very complete that they act as filters.

1. It has been found possible to pass under a microscope a cannula directly into the glomerular capsule (Richards and Wearn) and the fluid withdrawn has been found to be of the same composition as blood minus the non-filterable protein.

In a similar way the pressure necessary to stop the flow through the glomerular capillaries has been found. This is about 200 mm. water, and since the colloidal osmotic pressure of the blood is 100 it may be considered that a sufficient head of pressure is available.

2. Any increase of the osmotic pressure of the blood such as occurs in severe sweating tends to reduce the urine produced and any reduction by dilution such as occurs after drinking causes an increase of urine.

3. It has also been found by experiment that cooling the kidney or the administration of cyanides which reduce its vital functions tends to cause the organ to produce a urine which might be considered a simple ultra-filtrate of serum, the chloride content being higher and the creatinine content being lower than in normal urine. More urine is produced. The cooled kidney becomes a simple physical mechanism.

4. As might be expected, too, a rise of general arterial pressure increases the flow of urine provided the procedure causing the rise does not constrict the vessels of the kidney. This is seen in the accompanying table:—

Procedure.	General blood-pressure.	Renal vessels.	Kidney volume.	Urinary flow.
Division of spinal cord in neck	Falls to 40 mm.	Relaxed	Shrinks	Ceases
Stimulation of cord . . .	Rises	Constricted	Shrinks	Diminished
Stimulation of cord after section of renal nerves	Rises	Passively dilated	Swells	Increased
Stimulation of renal nerves	Unaffected	Constricted	Shrinks	Diminished
Stimulation of splanchnic nerve	Rises	Constricted	Shrinks	Diminished
Injection of normal saline	Rises	Dilated	Swells	Increased
Hæmorrhage	Falls	Constricted	Shrinks	Diminished

These results have been obtained also by Richards and Plant, who have shown that they are independent of the blood-flow. Similarly, increasing the pressure in the tubules by obstructing the out-flow of urine in a *denervated* kidney causes the production of urine similar in amount and quality to that produced after lowering the arterial pressure (Winton).

The amount, however, of urine does not depend wholly on the height of the blood-pressure; and one very striking fact in this relation may be mentioned now—namely, that if the blood-pressure is increased without allowing the blood to flow, the amount of urine formed is not increased; this can be done by ligaturing the renal vein; the blood-pressure within the kidney then rises enormously, but the flow of urine stops.

It has also been shown that substances may pass through the glomerular membrane in accordance with the size of their molecules, as would occur in the case of purely physical membrane. Protein and hæmoglobin are not normally excreted, but may appear if the glomerular epithelium becomes damaged by inflammatory states:

The formation of urine in the glomeruli is then almost identical with the production of tissue fluid and lymph but with the added activity of the tubules.

The Function of the Tubules.

Selective Reabsorption.—Since the kidney has two sets of capillaries in series, it is evident that the blood-pressure in the capillaries of the tubules must be less than in those of the glomeruli and that the effect of the osmotic pressure of the blood will be relatively greater in the tubules. The idea that the reabsorption of water might take place in the tubules had this anatomical basis and was put forward by Ludwig to account for the concentration of the urine.

The development of accurate chemical analysis of blood and urine showed, however, that the various substances which might be filtered off in the glomeruli must be absorbed to different extents, for it was found that they were not all concentrated to the same extent and that only some were finally excreted. Cushny and subsequently Richards and also Winton have put forward evidence of a selective reabsorption which depends on a vital activity of the cells of the tubules and which involves the use of oxygen. The substances which have fixed a concentration or threshold in the blood, such as sugar and chlorides and which are reabsorbed, are considered to be threshold substances and others which are fully excreted are non-threshold substances. (See Winton, 1937.)

The examination of minute specimens withdrawn directly from different parts of the tubules indicates that glucose is reabsorbed in the proximal part of the tubule and that water and chloride are reabsorbed chiefly in the distal part (White and Schmidt).

There is indeed some similarity between tubular and intestinal activity. Filtration and reabsorption are also recognised as occurring together in the case of the lymph. In early days there was some debate as to whether there was time for the urine to be concentrated in its passage down the tubules, but the number of tubules is so large that the amount necessarily absorbed by a tubule of 3 cms. in length need only be 1.4 mg. of water per day. Moreover, it has been found by direct tubular sampling that inulin when injected into the blood is excreted solely by the glomeruli and not reabsorbed, yet it is concentrated more than 100 times. This is adequate to account for the concentration of all other substances in the urine with the exception of those formed by the kidney (ammonia and hippuric acid). (See Richards, 1929).

Excretion.—The apparent failure of filtration and reabsorption to explain the concentration of the urine from a simple blood filtrate led originally to the view that certain substances such as urea and creatinine were "secreted" into the urine (Bowman).

That the tubules can act as purely excreting organs is seen in certain fishes in which glomeruli are absent yet normal urine is produced.

It has been found, too, that a kidney which is cooled, or which has been poisoned with cyanide which reduces oxidation processes, excretes less urea and sulphates, while there is an increase of chlorides and of water. This suggests that the vital mechanism

THE NEPHRON

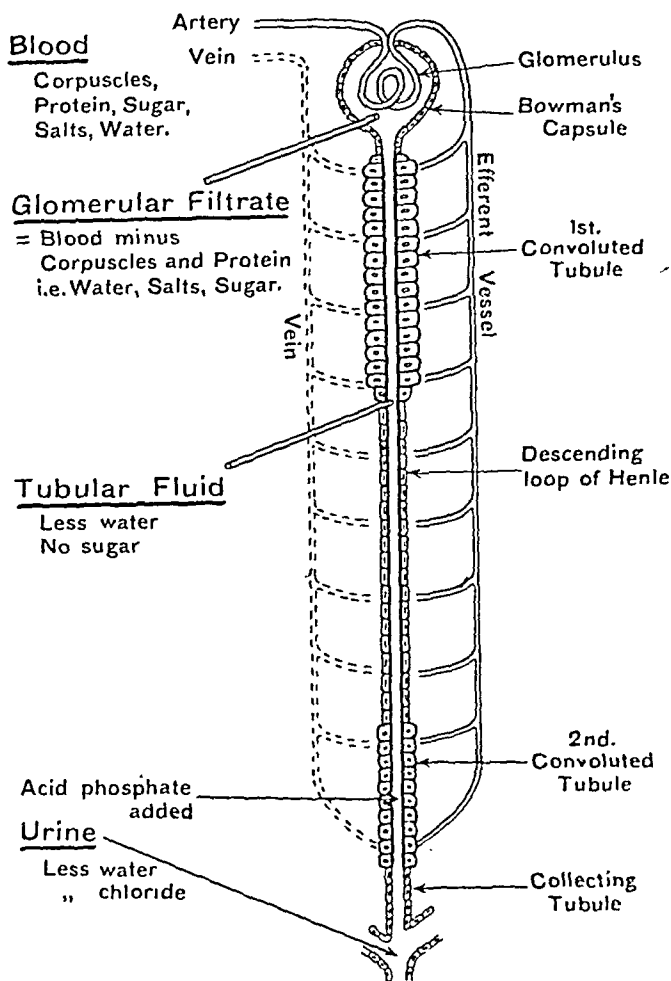


FIG. 174.—Diagram of the nephron of a mammal showing its chief features. The sizes of its various parts are necessarily out of proportion. For the size of glomerulus given the tubule should be several feet long.

for excretion of urea and sulphate and for absorption becomes impaired (Starling and Verney). Moreover, if the production of urine is prevented by raising the pressure in the ureters the injection of urea causes the production to recommence, a fact which is very difficult to explain by filtration and reabsorption.

Marshall also has found that the excretion of phenol-red in

dogs is much greater than can be obtained by the filtration of a solution of this substance in plasma through a collodion membrane having similar permeability to that of a glomerulus.

It is evident that the kidney can elaborate new substances such as hippuric acid from glycine and benzoic acid when the latter is administered. It can also form ammonium salts by breaking down urea when necessary to neutralise acids which may be added to the blood. In similar circumstances it forms acid sodium phosphate from organic phosphate and excretes a larger proportion than normally, and this function has by specimens taken direct from the tubules been located to a small region of the distal tubule.

This latter finding emphasises the specialised activity of certain of the tubules as their histological structure suggests and that it is quite reasonable to assume, as suggested by Bowman, that some cells of the tubules excrete or secrete and that others are more concerned with reabsorption. This is supported by the findings in disease in which it is found that the kidney's power to concentrate different substances may be appreciably impaired.

The various facts in regard to the composition of the urine are conveniently summarised in the above diagram of a single kidney unit, the nephron.

The comparative physiology of the kidney, which throws much light on its function, is well discussed by Marshall, 1934.

Extirpation of the Kidneys.

Extirpation of one kidney for tuberculosis, etc., is a common operation. It is not followed by any untoward result. The remaining kidney, if healthy, enlarges and does the work previously shared between the two. In dogs as much as a kidney and a half have been removed without any diminution of excretion.

Extirpation of both kidneys is fatal; the urea, etc., accumulate in the blood, and the animal dies in a few days; uræmic convulsions do not usually occur in such experiments.

Ligature of both renal arteries leads to the same result as extirpation. Partial compression of the renal arteries leads to the liberation into the blood of a substance *renin* which raises the blood-pressure. This probably accounts for the high blood-pressure in kidney disease.

The Control of Renal Secretion.

The Renal Nerves.—The renal plexus gets vasoconstrictor fibres from the sympathetic and dilator fibres probably from the vagus, but we do not know of true secretory nerves. Fibres from the anterior roots of the eleventh, twelfth, and thirteenth thoracic

nerves (in the dog) pass into this plexus. They are both vaso-constrictor and vasodilator in function. The nerve-cells on the course of the constrictor fibres are situated in the coeliac, mesenteric, and renal ganglia; the nerve-cells on the course of the dilator fibres are placed in the coeliac plexus and renal ganglia. The vagus also sends branches to the renal plexus (Cunningham). We have, at present, no knowledge of true secretory nerves to the kidney. The nerves just described affect the blood-vessels (Rose Bradford, Burton-Opitz) and the number of glomeruli in use, and also exert trophic (nourishing) functions.

The diuresis produced by the ingestion of a given amount of water is reduced by exercise (Pembrey) and sensory stimulation, but both have now been shown to occur in denervated as well as normal kidneys (Winton). There must be reciprocal control of the excretions of fluid by the skin and by the kidney, for the more we sweat the less urine is produced (see Water Balance); but this probably depends on the concentration of the blood.

In conclusion it may be stated in the light of present knowledge that the amount of urine produced depends on the capillary pressure in the glomerulus, the number of active glomeruli, and the composition of the blood.

The Antidiuretic Hormone of the Pituitary.—When the posterior lobe of the pituitary body, or that part of the hypothalamus which controls it, is damaged by disease or experimentally *diabetes insipidus*, there results a condition characterised by the production of large quantities of a dilute sugar-free urine and consequently great thirst. The condition is relieved by the administration of post-pituitary extract. Verney and his co-workers have demonstrated that when the blood is concentrated the pituitary secretes an anti-diuretic hormone. If the anterior lobe of the pituitary is removed as well diabetes insipidus does not result.

The Effect of Diet on Kidney Volume.

It has been found possible to study the volume of the kidney by exteriorising it outside the abdominal wall with all its essential connections intact (Allen and Cope, 1942) and it has been observed that the kidney increases considerably in size if the animal is given a high salt or a high protein diet. Prolongation of the latter led, however, to a true hypertrophy of kidney tissue, but the effect of a high salt diet and the increased blood-pressure which accompanied it passed off when a normal diet was resumed. These facts are important as they indicate how the kidney may respond to pathological states.

There occur also daily and even hourly variations in size of

the kidney during normal activity. These changes appear to be due to varying amounts of blood in the kidney and the use of varying numbers of nephrons.

Renal Efficiency.

The efficiency of the kidney may be judged conveniently by its power to eliminate urea. Two tests have been based on this function.

Urea Concentration Test (Maclean and de Wesselow).—From a study of the table on p. 516 it is evident that the kidney has the power of concentrating urea. This power is the basis of a useful test of kidney efficiency. After the administration of 15 grammes of urea in 100 c.c. of water, specimens of urine are taken one and two hours afterwards; the second specimen will contain above **2 per cent. urea** if the kidneys are acting normally. The factor obtained by dividing the concentration of urea in the urine by that in the blood is also an indication of the urea-concentrating power of the kidney, but the test takes longer. In severe kidney disease the figure, instead of being 90, may be reduced to 10.

The Urea Clearance Test (Van Slyke).—This test is based on the fact that the amount of urea excreted per day must be independent of the amount of urine passed, otherwise urea would accumulate in the body. On a given diet, therefore, the concentration of urea in the urine must vary with the dilution or the concentration of urine, that is, urea (U) multiplied by amount of urine (V) must be constant. But these factors must depend on the concentration of urea in the blood and the amount of blood which is theoretically cleared of urea (C) in passing through the kidney, *i.e.* $U \times V = B \times C$ where B = blood urea.

If, therefore, we know the concentration of urea in the blood (B) we know the amount of blood which must have been cleared of urea (C) theoretically in a given time, *i.e.* $\frac{UV}{B}$.

Thus with a blood urea of 0.03 per cent., a urine urea of 2 per cent. and a urine flow of 2 c.c. per minute, the amount of blood cleared of urea will be 133 c.c. Actually if the urine flow falls below 2 c.c. per minute, it has been found experimentally that the urine concentration varies as the square root of the volume and the clearance is therefore $\frac{U\sqrt{V}}{B}$.

In carrying out the test the bladder is emptied, a pint of water is taken and samples examined of urine passed $1\frac{1}{2}$ hours later.

Renal efficiency may also be judged by the power of the organ to excrete **dyes**. These tests give a more accurate indication of the

renal efficiency than the blood urea which does not accumulate until almost three-quarters of the renal tissue have been destroyed by disease, since the slightest accumulation merely acts as a diuretic to the remaining healthy parts. It appears that the power of the kidney to eliminate urea runs parallel with its capability of excreting dyes such as indigo-carmin and phenolsulphonaphthalein. The dye is injected intravenously and 70 per cent. is normally excreted in two hours.

Since anaesthesia may cause slight renal impairment to become serious, it is often important to perform such tests prior to an operation. Such tests are also carried out when attempts are being made to determine how far kidney disease has progressed, and what the future of the patient may be. Whenever possible the urea clearance test is to be preferred, but the specific gravity test is commonly sufficient (see p. 529).

Micturition.

As each portion of urine is secreted it propels that which is already in the uriniferous tubes onwards into the pelvis of the kidney. Thence, through the ureter, the urine passes into the bladder, into which its rate and mode of entrance have been watched by means of the cystoscope, or in patients in whom the lower anterior abdominal wall and the anterior wall of the bladder is absent. The urine does not enter the bladder at any regular rate, nor is there a synchronism in its movement through the two ureters. During fasting, two or three drops enter the bladder every minute; each drop as it enters first raises up the little papilla through which the ureter opens, and then passes slowly through its orifice, which at once closes again like a sphincter. Its flow is aided by the peristaltic contractions of the ureters, and is increased in deep inspiration, by straining, in active exercise, and in the first fifteen or twenty minutes after a meal. The urine is prevented from regurgitation into the ureters by the latter passing obliquely through the walls of the bladder and is retained in the organ by two rings of muscle at its exit, known as the internal and external sphincters, until voided.

The efferent nerves to the bladder are:—(1) *The nervi erigentes* which are parasympathetic. Stimulation of these nerves causes contraction of the bladder, and relaxation of its sphincter, the two necessary acts by which the urine is expelled. (2) *The hypogastric nerves* which are sympathetic; pre-ganglionic fibres leave the cord in the lumbar region, pass through to the inferior mesenteric ganglion; the post-ganglionic fibres are very short and synapse in cells near the bladder wall. Much difference of opinion has been expressed regarding the action of these nerves. The effect

of stimulation appears to depend on the degree of anæsthesia used and the degree of tension present. Stimulation of (1) or (2) causes contraction of the flaccid bladder and relaxation of the contracted bladder. In man, however, there is evidence of antagonism, for it has been found that difficult micturition resulting from lesions of the pelvic nerve is relieved by sympathetic section (Learmonth). On the other hand, a dose of the sympathetic drug ephedrine may in sensitive persons make micturition temporarily impossible, while atropine, the paralyrant of the parasympathetic, may be of value in the treatment of nocturnal bed-wetting in children.

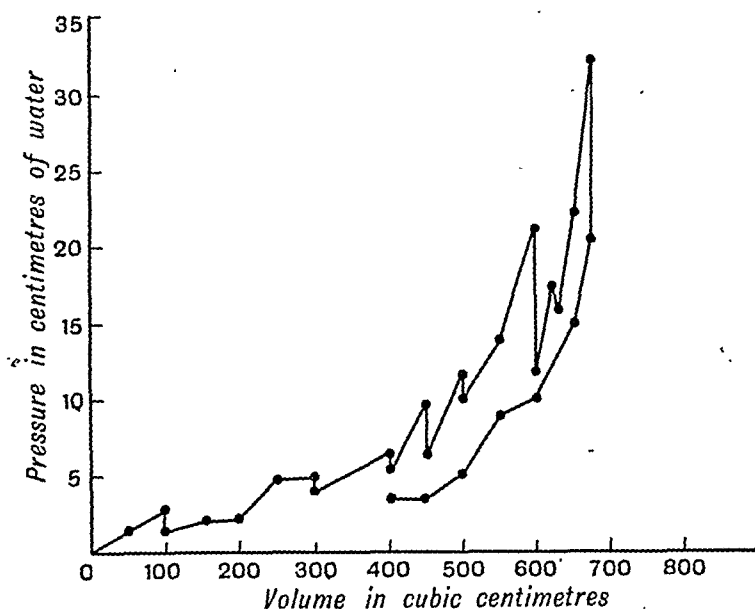


FIG. 175.—The changes in pressure which occur in the human bladder as it is filled with fluid (upper curve) and as it empties (lower curve). (Denny Brown and Robertson.)

Fundamentally, micturition may be considered a reflex act. It is so in young children in whom the bladder empties reflexly when the internal pressure rises. In the dog a pressure of 200 mm. of water initiates the reflex. The reflex is abolished by cocainising the bladder.

The afferent impulses so produced pass to the central nervous system by the pelvic nerves and set up a reflex through the hind-brain. There are, however, subsidiary arcs in the lumbo-sacral cord and these are able to take over control in man and animals if the spinal cord is injured higher up. The spinal tracts subserving micturition in man have been found to be the dorsal cerebellar (M'Michael and Dible).

Normally there is superimposed upon the basal reflexes a voluntary control. When the bladder is sufficiently full and

a certain internal tension reached there is a desire to micturate, but the point at which this occurs probably depends on the tone of the bladder, the composition of the urine, and the irritability of the bladder walls. If the desire is resisted the bladder relaxes slightly and the desire passes off. The pressure, however, does not quite return to its previous level, but there is adaptation of the bladder to its contents at a slightly higher pressure. This adaptation can be shown if fluid is injected into the bladder through a catheter, and is probably an adaptation to the needs of immediate physical exercise, for adrenaline has been shown to cause a marked relaxation. The intention to micturate or the sound of running water causes the bladder to contract and a rise in its internal pressure.

It is at first easy to ignore the desire to micturate but becomes increasingly difficult as the pressure in the bladder rises. Micturition from a half-full bladder is much more a voluntary act and in some circumstances is difficult. This is not to be confused with the difficulty in emptying an excessively full bladder which has become partially paralysed by the internal pressure.

Sometimes in young persons and in animals great difficulty is experienced in beginning micturition because of nervousness. The act is facilitated by the sound of running water or by placing the hands in water. This suggests that the normal retention of urine may become exaggerated reflexly and the view that the retention becomes a conditioned reflex is still further supported by the fact that a puppy in which the retention reflex is not fully formed may pass urine under the influence of an extraneous stimulus. This suggests the release of a conditioned inhibition. (Pavlov.)

After spinal injury voluntary control of the bladder is lost and if the urine is not drawn off the viscus fills and eventually overflows. If, however, the lumbo-sacral cord is intact, and the nursing has been sufficiently good to prevent infection of the urinary tract, after some weeks the primitive reflex emptying of the bladder may return.

The act of micturition in the adult consists of the relaxation of the external sphincters and contraction of the bladder assisted commonly by the contraction of the abdominal muscles. This results in a small quantity of urine reaching the upper part of the urethra, and this has been shown experimentally to set up a further set of reflexes which enhances the contraction and brings about full relaxation of the internal sphincters. Mechanical compression of a full bladder will bring about the reflex which appears to depend on pathways through the mid-brain, for it is absent if this part of the brain is cut off. At the commencement of micturition the pressure of urine in the bladder may reach 1000 mm. of water. Sometimes, especially if the neck of the bladder

has become irritable from the deposition of crystals precipitated from the urine, the contraction of this part may be so violent that there is discomfort or even intense pain. This is not uncommon in students as a result of the deposition of alkaline phosphates. It is relieved by rendering the urine acid—and the taking of diluents.

If urine is voided too frequently, the cause may be (1) *peripheral*, as in inflammation of the bladder; here the organ is unduly sensitive to the pressure of fluid; or (2) *central*, as in cases of fear and excitement; here the sensibility of the vesical centre is heightened.

The Action of Diuretics.

Diuretics are substances which increase the flow of urine and are used in dropsy, *i.e.* when water accumulates in the body as a result of a faulty circulation, or in certain varieties of kidney disease, but their action may also be demonstrated on normal people. From our study of the mechanism of the production of urine it is evident that they may act as follows:—

1. They may reduce the reabsorption in the tubules either (*a*) osmotically, *e.g.* urea, sodium sulphate, and like salts, or (*b*) by poisoning the cells of the tubules, *e.g.* the mercury salts (mersalyl being most used).

2. They may raise the general blood-pressure and increase the flow of blood through the kidney, *e.g.* digitalis, which stimulates and relieves the heart.

3. They may bring more glomeruli into action, *e.g.* caffeine.

REFERENCES.—Barrington and Langworthy; Kobb and Lewis.

CHAPTER XXXVII

THE URINE

Quantity.—A man of average weight and height produces from 1400 to 1600 c.c., or about 50 fluid oz. daily. The quantity, however, may vary enormously from day to day and from hour to hour according to the amount of fluid taken and to the amount of water excreted in other ways. If sweating is increased the quantity of the urine is correspondingly reduced. When metabolism is reduced to a minimum during sleep very little urine is secreted.

Colour.—This is some shade of yellow which varies considerably with the concentration of the urine. It is due to a mixture of pigments; of these the most abundant is a yellow one, named *urochrome*, of unknown chemical composition.

There are also several other pigments:—

Urobilin.—The bile pigment in the intestines is converted into stercobilin, most of which leaves the body with the faeces; some, however, is reabsorbed and is excreted into the urine, and is then called urobilin. It is normally present in small quantities only. Its precursor, a chromogen called urobilinogen, is colourless, but by oxidation—for instance, standing exposed to the air—is converted into the pigment proper, is more abundant than urobilin itself. In certain diseased conditions the amount of urobilin is considerably increased.

Uro-erythrin, the colouring matter of pink urate sediments, appears to be a small but constant constituent of urine, but its origin is unknown. Normal urine contains also a trace of *hæmatoporphyrin*, and the amount is increased in certain diseased states.

Reaction.—The reaction of normal urine is acid; this is due mainly to acid salts, of which acid sodium phosphate is the most important. The reaction of the urine is normally from $\text{pH } 7$ to $\text{pH } 5.5$. It is more acid on an acid-producing diet such as meat and fat, but the acidity increases after exercise and when abnormal acids are taken or are produced during metabolism as in diabetes. Under certain conditions the urine becomes less acid and even alkaline; the most important of these are as follows:—

1. A diet of fruit and vegetables contains an excess of salts of organic acids, *e.g.* citric, tartaric, which are oxidised to carbonates and make the urine alkaline. Whole cereals, *e.g.* rice, like meat

cause an acid urine because of the sulphur they contain. The reaction of the urine has a very considerable practical importance. In an alkaline urine phosphates are likely to precipitate and cause irritation of the neck of the bladder and bacteria are liable to flourish. In infections of the urinary tract the treatment consists of making the urine very acid and to secure this the diet is of primary importance. Acid sodium phosphate, ammonium chloride, and mandelic acid are given also for this purpose, but such drugs are of no value unless strict attention is paid to the diet. Of recent years a ketogenic diet composed largely of fat and meat with insufficient carbohydrate has been much used, but for some unexplained reason normal persons adapt themselves—like Eskimos—and burn fat fully. Whenever the acidity of the urine changes there is also a change in the ammonia-urea ratio. (See below.)

2. During digestion and in the forenoon. Here there is a formation of free acid in the stomach, and a corresponding liberation of bases in the blood, which, passing into the urine, diminish its acidity, or even render it alkaline. This is called *the alkaline tide*. Leathes considers that respiration is more important than gastric secretion in the forenoon in producing the change. During sleep respiration is comparatively inactive; hence carbon dioxide accumulates, and the resulting rise in H-ion concentration is reflected in the urine. With the activity associated with daytime this effect passes off.

Specific Gravity.—This varies inversely as the quantity of urine passed under normal conditions from 1015 to 1025. A specific gravity below 1010 should excite suspicion of hydruria or diabetes insipidus; one over 1030, of a febrile condition, or of diabetes mellitus, in which it may rise to 1050. The specific gravity has, however, been known to sink as low as 1002 (after large potations, *urina potus*), or to rise as high as 1035 (after great sweating and after sleep) in perfectly healthy persons.

The specific gravity of the urine passed first thing in the morning is also an indication of the efficiency of the kidney.

Kidneys which are capable of producing a good amount of night urine with a specific gravity of 1025 or over must have glomeruli capable of excreting a reasonable amount of salts and tubules capable of concentrating them. A dilute night urine in the absence of fluid intake at bed-time suggests that the kidney has difficulty in excreting salts, and more elaborate efficiency tests may be needed if a surgical operation is contemplated.

Composition.—The following table gives the average amounts of the urinary constituents passed by a man taking an ordinary diet containing about 100 grams of protein in the twenty-four hours,

but it must be realised that many of the constituents may vary appreciably from hour to hour:—

	Grams		Grams
Total quantity of urine	1500·00	Sulphuric acid	2·0
Water	1440·00	Ammonia	0·65
Solids	60·00	Creatinine	0·9
Urea	35·00	Chlorine	11·0
Uric acid	0·75	Potassium	2·5
Hippuric acid	0·7	Sodium	5·5
Sodium chloride	16·5	Calcium	0·26
Phosphoric acid	3·5	Magnesium	0·21

The most abundant constituents of the urine are water, urea, and sodium chloride. In the foregoing table one must not be misled by seeing the names of the acids and metals separated. The acids and bases are combined to form salts, such as urates, chlorides, etc.

It is important to note that the constituents of urine, with the exception of acid sodium phosphate, hippuric acid and ammonia, are not formed by the kidney but that the kidney merely excretes them from the blood.

The nitrogenous constituents, urea, ammonia, uric acid, hippuric acid, are the products of exogenous and endogenous protein metabolism. The creatinine and part of the sulphuric acid (neutral sulphur) are the products of endogenous metabolism and are not affected by variation in the amount of protein in the diet.

Urea.

The origin of urea from amino-acids has already been dealt with (p. 491). The urea arising from the exogenous metabolism of protein is normally greater than that arising from endogenous metabolism, and varies in quantity directly with the protein of the diet. In a man in a state of nitrogenous equilibrium, taking daily 100 to 120 grams of protein in his food, the quantity of urea excreted daily is about 33 to 35 grams (500 grains). The percentage in human urine is usually 1·5-2 per cent.; but this varies, because the concentration of the urine varies considerably in health. The excretion of urea is usually at a maximum three hours after a meal, especially after a meal rich in proteins. In those who adopt a reduced protein diet, Folin has shown that the decrease in urinary nitrogen falls mainly on the urea fraction, and in some cases the urea excreted accounted for only 66 per cent. of the total nitrogen. The other nitrogenous katabolites of the urine alter comparatively little under such conditions, and the creatinine in particular remains remarkably constant in amount.

The time-honoured structural formula of urea as carbamide $\text{CO} \begin{smallmatrix} \diagup \text{NH}_2 \\ \diagdown \text{NH}_2 \end{smallmatrix}$ may now be said to have gone into the melting-pot and

it is most likely that it cannot be represented by any single static formula, for reasons already discussed in relation to the origin of urea. Urea has the same empirical formula as ammonium cyanate (NH_4CNO), from which it was first prepared synthetically by Wöhler in 1828. Since then it has been prepared synthetically in other ways. Wöhler's observation derives interest from the fact that this was the first organic substance ever prepared synthetically by chemists.

Urea is readily soluble both in water and alcohol: it has a saltish taste, and is neutral to litmus paper.

The form of its crystals is shown in fig. 176. When treated with nitric acid, nitrate of urea ($\text{CON}_2\text{H}_4 \cdot \text{HNO}_3$) is formed; this crystallises in octahedra, lozenge-shaped tablets, or hexagons. When treated with oxalic acid, prismatic crystals of urea oxalate ($\text{CON}_2\text{H}_4 \cdot \text{H}_2\text{C}_2\text{O}_4 + \text{H}_2\text{O}$) are formed. These crystals may be readily obtained by adding excess of the respective acids to urine which has been concentrated to a third or a quarter of its bulk.

Under the influence of a micro-organism, the *micrococcus ureæ*, which grows readily in stale urine, urea takes up water, and is converted into ammonium carbonate [$\text{CON}_2\text{H}_4 + 2\text{H}_2\text{O} = (\text{NH}_4)_2\text{CO}_3$]. Hence the ammoniacal odour of putrid urine.

By means of nitrous acid, urea is broken up into carbonic acid, water, and nitrogen, $\text{CON}_2\text{H}_4 + 2\text{HNO}_2 = \text{CO}_2 + 3\text{H}_2\text{O} + 2\text{N}_2$. The evolution of gas bubbles which takes place on the addition of fuming nitric acid* may be used as a test for urea.

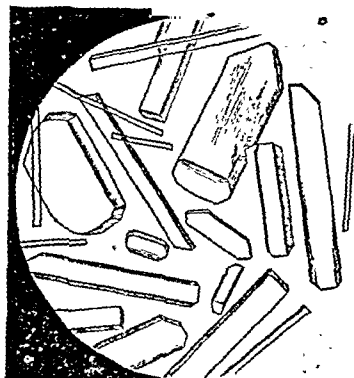
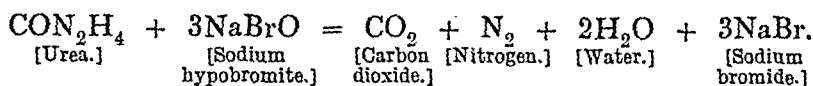


FIG. 176.—Crystals of urea.

The main reaction between sodium hypobromite and urea may be represented thus:—



Side reactions of a complex nature also occur, and a small amount (less than 1 per cent.) of carbon monoxide is mixed with the nitrogen, but the reaction may be used as a rough-and-ready method for estimating urea (see p. 544).

Uræmia.—This is the term given to the dangerous state commonly associated with unconsciousness which results from severe disease of the kidney. The term was originally applied on the erroneous supposition that it is urea or some antecedent of urea which acts as the poison. There is no doubt that the poison is not any constituent of normal urine; if the kidneys of an animal are extirpated, the animal dies in a few days, but there are no uræmic convulsions. In man, also, if the kidneys are healthy, or approximately so, and suppression of urine

* Fuming nitric acid contains nitrous acid in solution.

occurs from the simultaneous blocking of both renal arteries by clot, or of both ureters by stones, again uræmia does not follow. On the other hand, uræmia may occur even while a patient with diseased kidneys is passing a considerable amount of urine. What the poison is that is responsible for the convulsions and coma is unknown. It is doubtless some abnormal katabolic product, but whether this is produced by the kidney cells, or in some other part of the body, is also unknown.

Ammonia.

The ammonia of the urine arises from the amino portion of deaminised amino-acids. A small amount reaches the kidney direct from the tissues, but the majority appears to be formed in the kidney from the breakdown of urea. In man the daily amount of ammonia excreted varies between 0·3 and 1·2 grams. The ingestion of ammonium carbonate does not increase the amount of ammonia in the urine, but increases the amount of urea, into which substance the ammonium carbonate is easily converted. But if a more stable salt, such as ammonium chloride, is given, it may appear as such in the urine. Some of the ammonia may, however, be converted into urea, and the hydrochloric acid may bring about a marked acidosis (Haldane) if sufficient ammonium chloride is taken.

The Ammonia-Urea Ratio.—The ammonia in the urine is not to be considered as a residue from the formation of urea, for this process is very complete. Rather it is the amount of ammonia which the kidney needs to neutralise acid. Since, however, the kidney obtains the ammonia from urea and amino-acids the more ammonia is excreted in the urine the less urea there will be. Normally, on a mixed diet the ratio is about 1:50. This indicates the amount of acid to be got rid of. When the production of acid is excessive, as in diabetes, excess of ammonium salts appears in the urine. A diminution in the output of ammonia occurs when there is an excess of alkali in the body. This takes place when alkali is administered, or on a vegetable diet. A decrease in the ammonium salts is accompanied by an increased alkalinity of the urine, since more alkali or less acid phosphate is excreted. That the ammonia is formed in the kidney is shown (Benedict) by the facts that if the kidneys are removed there is a reduction of the ammonia of the blood and that there is normally more ammonia in the renal venous blood than in the arterial. This view is supported by the fact that in the acidæmia due to kidney disease the ammonia-urea ratio does not change (McLean), while it has been found that if the liver is removed there is no appreciable change in the amount of ammonia excreted by the urine.

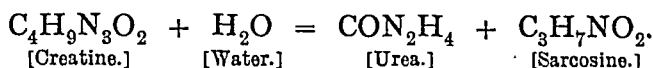
It is of interest that if ammonium chloride is given to a herbivorous animal such as a rabbit, the urinary ammonia is but little increased. It reacts with sodium carbonate in the tissues, forming ammonium carbonate (which is excreted as urea) and sodium

chloride. Herbivora also suffer much more from, and are more easily killed by, acids than carnivora, their organisation not permitting a ready supply of ammonia to neutralise excess of acids.

It is important to emphasise that all that has been said in regard to ammonia refers to urine freshly passed. All urine, if allowed to stand, becomes ammoniacal, as a result of the breakdown of urea by the *micrococcus ureæ*.

Creatine and Creatinine.

Creatine is a constant constituent of muscle; its chemical structure is very like that of arginine; it contains a urea radical, and when boiled with baryta it splits into urea and sarcosine (methyl-glycine), as shown in the following equation:—

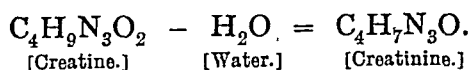


At present the evidence appears to be that the muscle does not make creatine but becomes saturated with it from the blood.

Creatine is absent from normal urine, but it is present in the urine during starvation, in acute fevers, in women during involution of the uterus, in the urine of infants, and in certain other conditions in which there is rapid loss of muscular material. If it is administered by the mouth large amounts are retained and if given in excess only about $\frac{1}{40}$ appears in the urine.

Its normal fate in the body is unknown; it may be converted into urea as in the foregoing equation, but injection of creatine into the blood-stream does not cause any increase in urea formation; the creatine injected is almost wholly excreted unchanged but a proportion is stored in the muscles.

Its normal origin is uncertain, but its excretion is much increased if glycine or glycine-rich proteins are fed (Brand). Creatine is readily convertible into creatinine as shown in the following equation:—



The rôle of creatine-phosphate in muscle contraction has already been discussed. (See Chemical Changes in Muscle.)

Creatinine, on the other hand, is an end-product, probably of muscle metabolism. From 0.8 to 1.3 grams are excreted in the urine in twenty-four hours; it is, in fact, next to urea, the most abundant nitrogenous substance in urine. The actual amount excreted is apparently proportional to the weight of the individual, especially to the muscular tissue possessed. It is the urinary constituent most constant in amount, diet having no effect on it,

i.e. it comes from endogenous metabolism. The problem was studied particularly by E. Mellanby. By improved methods he showed that creatinine as such is never present in muscle at all, even after prolonged muscular work. He then studied in the developing bird the amount of creatine at different stages, and found that it is entirely absent in the chick's musculature up to the twelfth day of incubation; after this date the liver and the muscular creatine develop *pari passu*. After hatching, the liver still continues to grow rapidly, and the creatine percentage in the muscles increases also, although the development in the size of the muscles occurs very slowly. Moreover, ingested creatinine is not stored like creatine but is excreted unchanged. It would seem then that certain products of protein katabolism, the nature of which is uncertain, are carried by the blood to the liver, and from these the liver forms creatine; this is transported to the muscles and there stored as creatine-phosphoric acid; when the muscles are saturated with creatine, excess of creatinine is then excreted by the kidneys. Its formation by the liver from amino-acids is suggested by the small amount excreted in diseases of that organ.

During muscular exercise the creatinine of the urine is increased and afterwards is equally diminished, but the daily excretion is increased by training. This suggests that when creatine is set free in the muscles by the breakdown of creatine-phosphate some becomes converted into creatinine, but that subsequently some is resynthesised to creatine-phosphate.

Blood Creatinine.—Normally this is 1 to 2 mg. per 100 c.c. but figures over 3 mg. are found in kidney disease. High values, over 5 mg., indicate an early death in chronic inflammation of the kidney. (Hunter, 1928.)



Fig. 177.—Various forms of uric acid crystals.

Uric Acid.

Uric Acid ($C_5N_4H_4O_3$) is, in mammals, the medium by which a very small quantity of nitrogen is excreted from the body. It is, however, in birds and some reptiles the principal nitrogenous constituent of their urine. In an acid urine it may be precipitated, but in an alkaline urine it occurs as urates. (See Purine Metabolism.)

It may be obtained from human urine by adding 5 c.c. of hydrochloric acid to 100 c.c. of the urine, and allowing the mixture to stand for twelve to twenty-four hours. The pure acid crystallises in colourless rectangular plates or prisms. In

striking contrast to urea it is almost an insoluble substance. The forms which uric acid assumes when precipitated from human urine, either by the addition of hydrochloric acid or in certain pathological processes, are very various, the most frequent being the whetstone shape; there are also bundles of crystals resembling sheaves, barrels, and dumb-bells (see fig. 177).

The **murexide** test is the principal test for uric acid. The test has received the name on account of the resemblance of the colour to the purple of the ancients, which was obtained from certain snails of the genus *Murex*. It is performed as follows: place a little uric acid or a urate in a capsule; add a little dilute nitric acid and evaporate to dryness. A yellowish-red residue is left. Add a little ammonia carefully, and the residue turns violet; this is due to the formation of purpurate of ammonia. On the addition of potash the colour becomes bluer.

Urates.—Uric acid does not contain the carboxyl group (COOH) which is typical of organic acids, and its reaction is neutral. Nevertheless its hydrogen atoms are replaceable, and it acts therefore as an acid, and forms *biurates* ($\text{MH}\bar{\text{U}}$). In the presence of strong bases it forms neutral *urates* ($\text{M}_2\bar{\text{U}}$), which, however, only exist in the solid condition, or in the presence of strong alkali; by water they are decomposed at once into primary urate and alkali.

In the urine and in blood are biurates mixed with uric acid ($\text{MH}\bar{\text{U}} \cdot \text{H}_2\text{U}$), the so-called quadriurates (Roberts). In gout the urates of the blood are increased and may be converted into less soluble isomeric forms which become deposited in the joints and other tissues.

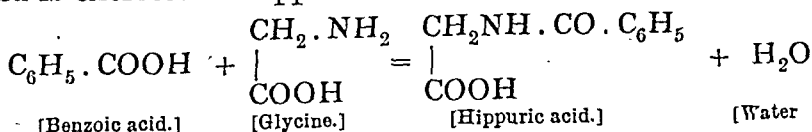
The quantity of uric acid excreted by an adult varies from 0.5 to 0.75 gram daily.

The **origin of uric acid** is dealt with under Purine Metabolism. The acid is formed not in the kidneys, but as the result of metabolic processes occurring elsewhere, since if the kidneys are removed, uric acid continues to be formed and accumulates in the blood and organs.

Man and the anthropoid ape are peculiar in that they excrete uric acid without further oxidation, but for some completely obscure reason this is true of the pure-bred Dalmatian coach hounds, although not of other dogs.

Hippuric Acid.

Hippuric Acid ($\text{C}_9\text{H}_9\text{NO}_3$), combined with bases to form hippurates, is present in small quantities in human urine, but in large quantities in the urine of herbivora. This is due to the food of herbivora containing substances belonging to the aromatic group—the benzoic acid series. If benzoic acid is given to a man, it unites with glycine with the elimination of a molecule of water, and is excreted as hippuric acid.



This is a well-marked instance of synthesis carried out in the animal body, and experimental investigation shows that it is accomplished by the living cells of the kidney itself; for if a mixture of glycine, benzoic acid, and blood is injected through the kidney (or mixed with a minced kidney just removed from the body of an animal), hippuric acid is found to have been formed. In the conversion of benzoic into hippuric acid which occurs in herbivora, the necessary glycine comes from the kidney itself.

The Inorganic Constituents of Urine.

The inorganic or mineral constituents of urine are chiefly chlorides, phosphates, sulphates, and carbonates; the metals with which these are in combination are sodium, potassium, ammonium, calcium, and magnesium. The total amount of these salts varies from 19 to 25 grams daily. The most abundant is sodium chloride, which averages in amount 10 to 16 grams per diem. These substances are derived from two sources—from the food, and as the result of metabolic processes.

Chlorides.—The chief chloride is that of sodium. The ingestion of sodium chloride is followed by its appearance in the urine, some on the same day, some on the next. Some is decomposed to form the hydrochloric acid of the gastric juice. The salt in the body fulfils the useful office of stimulating metabolism and secretion.

Sulphates.—The sulphates in the urine are principally those of potassium and sodium, and arise normally from the sulphur-containing amino-acid cystine and its decomposition product ethyl mercaptan (C_2H_5SH). The sulphates vary in amount from 1.5 to 3 grams daily. (See Lewis, 1924.)

The sulphur of the proteins of the diet in passing through the liver becomes completely oxidised to form *inorganic sulphates*. That however which is derived from breakdown of cystine of body proteins for the most part escapes the liver, which from the circulatory point of view is parallel to the kidney and is not converted into ordinary sulphates to any great extent, but appears in the urine partly as ethereal sulphates, and partly as certain obscure but not fully oxidised sulphur compounds*; it is usually spoken of as *neutral* or *unoxidised sulphur*, which therefore, like creatinine, bears a direct relation to endogenous metabolism.

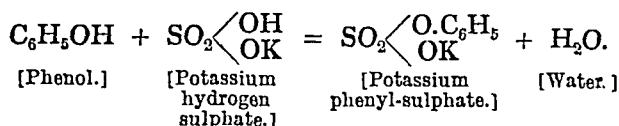
The *ethereal sulphates* just mentioned form about a tenth of the total sulphates. They are combinations of sulphuric acid with organic radicals, and the greater part of them originate from putrefactive changes in the intestine. The chief of these ethereal

* These include cystine, oxyproteic acid, alloxypoteic acid, and methyl mercaptan.

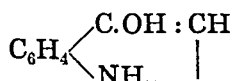
sulphates are phenyl-sulphate of potassium and indoxyl-sulphate of potassium. The latter originates from the indole formed in the intestine, and as it yields indigo when treated with certain reagents it is sometimes called *indican*.

The formation of these sulphates is important; the aromatic substances liberated by putrefactive processes in the intestine are poisonous, but their conversion into ethereal sulphates renders them harmless.

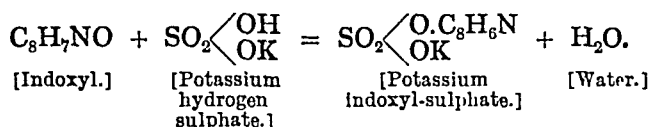
The equation representing the formation of potassium phenyl-sulphate is as follows:—



Indole ($\text{C}_8\text{H}_7\text{N}$) on absorption is converted into indoxyl:—



The equation representing the formation of potassium indoxyl-sulphate is as follows:—



Carbonates.—Carbonates and bicarbonates of sodium, calcium magnesium, and ammonium are present only in alkaline urine. They arise from the carbonates of the food, or from vegetable acids (malic, tartaric, etc.) in the food. They are therefore found in the urine of herbivora and vegetarians, whose urine is thus rendered alkaline. Urine containing carbonates becomes, like saliva, cloudy on standing, the precipitate consisting of calcium carbonate and also phosphates.

Phosphates.—Two classes of phosphates occur in normal urine, but the actual salts found depend on the reaction of the urine.

(1) Alkaline phosphates—that is, phosphates of sodium (abundant) and potassium (scanty).

(2) Earthy phosphates—that is, phosphates of calcium (abundant) and magnesium (scanty).

The composition of the phosphates in urine is liable to variation. In acid urine the acidity is due chiefly to the acid salts, sodium dihydrogen phosphate, NaH_2PO_4 , and calcium dihydrogen phosphate, $\text{Ca}(\text{H}_2\text{PO}_4)_2$.

In alkaline urine the alkaline phosphates, disodium hydrogen phosphate, Na_2HPO_4 , calcium hydrogen phosphate, CaHPO_4 , and magnesium hydrogen phosphate, MgHPO_4 , predominate. In neutral urine there is a mixture of the acid and alkaline salts.

The earthy phosphates are precipitated by rendering the urine

alkaline by ammonia. In decomposing urine, ammonia is formed from the urea. The phosphates are precipitated as a white creamy precipitate of:—

(1) Triple phosphate or ammonio-magnesium phosphate ($\text{NH}_4\text{MgPO}_4 + 6\text{H}_2\text{O}$). This crystallises in "coffin-lid" knife-rest crystals (see fig. 178) or feathery stars.

(2) Stellar phosphate, or calcium phosphate; this crystallises in star-like clusters of prisms.

As a rule normal urine gives no precipitate when it is boiled; but sometimes neutral, alkaline, and occasionally faintly acid urines give a precipitate of calcium phosphate when boiled because of the dissolved CO_2 being driven off: this precipitate is amorphous, and is liable to be mistaken for albumin. It may be distinguished readily from albumin, as it is soluble in a few drops of acetic acid, whereas coagulated protein does not dissolve.

The urinary phosphates originate from the phosphates of the food, but are partly decomposition products of the phosphorised organic materials in the body, such as lecithin and nuclein. It has been found that to supply this waste a supply of 2.25 grams PO_4 is necessary but the diet is not usually deficient and the amount of P_2O_5 in the twenty-four hours' urine varies from 2.5 to 3.5 grams, of which the earthy phosphates contain about half (1 to 1.5 gr.). The urine also contains minute quantities of organic phosphates, for instance, glycestro-phosphates.

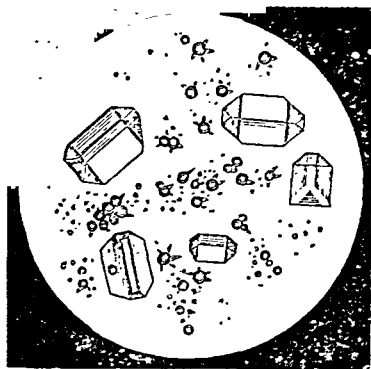


FIG. 178.—Urinary sediment of triple phosphates (large prismatic crystals) and urate of ammonium, from urine which had undergone alkaline fermentation.

Tests for the Inorganic Salts of Urine.—

Chlorides.—Acidulate with nitric acid and add silver nitrate; a white precipitate of silver chloride, soluble in ammonia, is produced. The object of acidulating with nitric acid is to prevent phosphates being precipitated by the silver nitrate.

Sulphates.—Acidulate with hydrochloric acid, and add barium chloride. A white precipitate of barium sulphate is produced. Hydrochloric acid is again added first, to prevent precipitation of phosphates.

Phosphates.—i. Add ammonia; a white crystalline precipitate of earthy (that is, calcium and magnesium) phosphates is produced. This becomes more apparent on standing. The alkaline (that is, sodium and potassium) phosphates remain in solution. ii. Mix another portion of urine with half its volume of nitric acid; add ammonium molybdate, and boil. A yellow crystalline precipitate falls. This test is given by both classes of phosphates.

Urinary Deposits.

The formed or anatomical elements may consist of blood-corpuscles, pus, mucus, epithelium cells, spermatozoa, casts of the

urinary tubules, prostatic threads, fungi, and entozoa. All of these, with the exception of a small quantity of spermatozoa and mucus, which forms a flocculent cloud in the urine, are pathological, and the microscope is chiefly employed in their detection.

The **chemical substances** are uric acid, urates, calcium oxalate, calcium carbonate, and phosphates. Rarer forms are leucine, tyrosine, xanthine, and cystine. These are of considerable importance in medicine, as their formation in the urinary passages may lead to the formation of "stone" or of "gravel," which leads to obstruction or to pain. The recognition and treatment of the condition depends on the microscopical examination of the deposits. We shall, however, here consider only the commoner varieties.

Deposit of Uric Acid.—This is a sandy reddish deposit resembling cayenne pepper, occurring in an acid urine. It may be recognised by its crystalline form (fig. 177, p. 534) and by the murexide reaction. The presence of these crystals generally indicates an increased formation of uric acid, which, if excessive, may lead to the formation of stones or calculi in the kidney and bladder.

Deposit of Urates.—This "brick dust" deposit is much commoner than uric acid, and may occur in concentrated normal

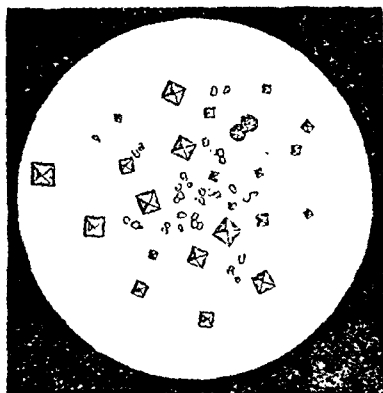


FIG. 179.—Crystals of calcium oxalate.

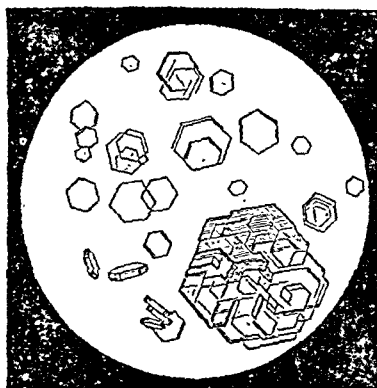


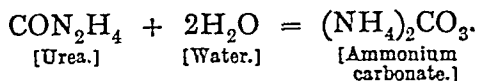
FIG. 180.—Crystals of cystine.

urine when it cools. It is generally found in the concentrated urine of fevers; and there appears to be a kind of fermentation, called the acid fermentation, which occurs in the urine after it has been passed, and which leads to the same result. It has a pinkish colour due to the pigment *uro-erythrin*, and dissolves upon warming the urine. It is usually amorphous, but crystalline forms similar to those depicted in fig. 178 may occur. Crystals of calcium oxalate may be mixed with this deposit (see fig. 179).

Deposit of Calcium Oxalate.—This occurs in envelope crystals (octahedra) or dumb-bells. It is insoluble in ammonia, and in acetic acid. It is soluble with difficulty in hydrochloric acid. Calcium oxalate calculi are the commonest kind of stones found in the kidney.

Deposit of Cystine.—Cystine ($C_6H_{12}N_2S_2O_4$) is recognised by its colourless six-sided crystals (fig. 180). These are rare: they occur only in acid urine, and they may form concretions or calculi. Cystinuria (cystine in the urine) is hereditary.

Deposit of Phosphates.—These occur in alkaline urine. The urine may be alkaline when passed, due to fermentative changes occurring in the bladder. All urine, however, if exposed to the air (unless the air is perfectly pure, as on the top of a snow mountain) will in time become alkaline, owing to the growth of the *micrococcus ureæ*. This forms ammonium carbonate from the urea.



The ammonia renders the urine alkaline and precipitates the earthy phosphates.

All these phosphates are dissolved by acids, such as acetic acid, without effervescence.

A solution of ammonium carbonate (1 in 5) eats magnesium phosphate away at the edges: it has no effect on the triple phosphate. A phosphate of calcium ($\text{CaHPO}_4 + 2\text{H}_2\text{O}$) may occasionally be deposited in acid urine. Pus in urine is apt to be mistaken for phosphates, but can be distinguished by the microscope.

Deposit of Calcium Carbonate, CaCO_3 , appears but rarely as whitish balls or biscuit-shaped bodies. It is commoner in the urine of herbivora. It dissolves in acetic or hydrochloric acid, with effervescence.

PATHOLOGICAL URINE.

Under this head we shall briefly consider only those abnormal constituents which are most frequently met with.

Proteins.—There is no protein in normal urine, and the most common cause of the appearance of albumin in the urine is disease of the kidney (Bright's disease). The term "albumin" is the one used by clinical observers. Properly speaking, it is a mixture of serum albumin and serum globulin.

Tests.—(1) *Heat*—Boil the top layer of half a test-tubeful of urine. If protein is present a cloud or a denser coagulum appears. The urine, if not already acid, should be previously acidified with acetic acid, as otherwise a cloud of phosphate may appear on heating because of expulsion of CO_2 ; the cloud of phosphate is soluble in acetic acid. (Compare Pus below.)

(2) *Nitric Acid* (Heller).—Run a drop of cold, concentrated nitric acid down the side of a test-tube containing a little urine. If protein is present a precipitate appears round the drop.

(3) *Salicylsulphonic acid* causes a white precipitate in the cold if protein is present.

Glucose.—Normal urine contains no sugar or so little that for clinical purposes it may be considered absent. The conditions in which glycosuria occurs are described on p. 480. Diabetic urine may contain, for reasons described in relation to the metabolism of fat (p. 489), **acetone** and **aceto-acetic** or **diacetic acid**. The presence of the aceto-acetic acid is specially important on account of its toxicity, and it indicates also the probable presence of β -**hydroxybutyric acid**. The specific gravity of a urine containing sugar is high.

Tests for Glucose.—(1) Take 5 c.c. of Benedict's solution and add 8 drops of urine and boil for 10 minutes. Greenish turbidity with small red deposit on standing = trace. Precipitates indicate amounts—greenish-yellow +, yellow ++, orange + + +, brick-red + + + +.

(2) The fermentation test. Half fill a test-tube with the urine and add a little yeast. Fill up the tube with mercury; invert in a basin of mercury, and leave it in a warm place for twenty-four hours. The sugar will undergo fermentation: carbonic acid gas accumulates in the tube, and the liquid no longer gives the tests for sugar, or only faintly, but gives those for alcohol instead. The specific gravity falls. The *phenyl-hydrazine* test may also be applied to distinguish between glucose, lactose, and pentose.

The following **Fallacies** in Fehling's test should be noted:—

(1) Lactose may occur in the urine of nursing mothers.

(2) Fructose, pentoses, and other sugars are found but rarely. Pentoses occur in certain individuals after the eating of certain fruits, apples, plums, cherries, and turnips, and sometimes after beer.

(3) Glycuronates.—These are present when the body is getting rid of certain abnormal substances, *e.g.* phenols formed from intestinal decomposition, or certain drugs, chloral, camphor, salicylates, chloroform, turpentine, morphine. These substances become linked to glycuronic acid ($C_6H_{10}O_7$), an oxidation product of glucose. The terminal CHO is free and reduces the copper like glucose itself. This, like the formation of ethereal sulphates, is an example of protective synthesis and appears to occur in the liver.

(4) Homogentisic Acid.—This occurs in the rare condition of *alkaptonuria*, which results from the faulty metabolism of tyrosine. The urine if exposed to the air becomes dark.

Discolorisation of the Fehling's solution, usually without actual reduction, may be caused by excess of urates or creatinine.

Rother's Test for Acetone.—Saturate the urine with ammonium sulphate, so as to leave some crystals undissolved at the bottom of the tube. Add a few drops of a fresh dilute solution of sodium nitroprusside and a little 10 per cent. ammonia. Acetone gives a purple permanganate coloration. If the colour develops rapidly and deeply, aceto-acetic acid is also present.

Test for Aceto-acetic Acid.—Ferric chloride gives a wine-red colour which is destroyed by boiling. Aceto-acetic acid results from faulty fat metabolism, and may therefore be present in diabetes, starvation, and hypoglycæmia produced by insulin.

Bile.—This occurs in jaundice. The urine is dark-brown, greenish, or in extreme cases almost black in colour.

Gmelin's test for bile *pigments* consists in a play of colours—green, blue, red, and finally yellow, produced by the oxidising action of fuming nitric acid (that is, nitric acid containing nitrous acid in solution). The end or yellow product is called *choletelin*, $C_{32}H_{36}N_4O_{12}$. The test is carried out by dipping a piece of filter paper into the urine, allowing it to dry and placing on it a small drop of the acid.

Hay's sulphur test for bile *salts*. If some flowers of sulphur (*i.e.* finely powdered) are sprinkled on the surface of normal urine they remain floating on the top. If bile salts are present even in small quantities, the fine sulphur particles fall down to the bottom of the vessel in which the urine is contained; this is due to a lowering of surface tension which bile salts produce.

Blood.—When hæmorrhage occurs in any part of the urinary tract, blood appears in the urine. If a large quantity is present the urine is deep red, if a small quantity only occurs then the urine looks "smoky." Microscopic examination then reveals the presence of blood-corpuscles, and on spectroscopic examination the bands of oxyhæmoglobin are seen. The urine also contains albumin.

The blood pigment may, under certain conditions, appear in the urine without the presence of any blood-corpuscles at all. This is produced by a disintegration of the corpuscles occurring in the circulation. The condition so produced is called *hæmoglobinuria*; it occurs in several pathological states, as for instance in the tropical disease called "Black-water fever." The pigment is in the condition of methæmoglobin mixed with more or less oxyhæmoglobin, and the spectroscope is the means used for identifying these substances.

Test for Blood Pigment.—To a little urine in a test-tube add a few drops of guaiaconic acid (or of tincture of guaiacum, which is less sensitive); shake, and add an equal quantity of ether containing hydrogen peroxide. The presence of blood is shown by a blue ring at the junction of the two fluids. The blue colour is due to oxidation of the guaiaconic acid by hydrogen peroxide in the presence of hæmoglobin. The test is given by saliva, which contains peroxidases; these are destroyed by boiling; solutions of hæmoglobin (or blood) still give the test after they have been boiled.

The urine of a patient who is taking iodides gives the guaiacum reaction, even after the urine has been boiled.

Benzidine test.—A knife point of benzidine is dissolved in 3 c.c. glacial acetic acid and 10 drops of this mixed with 3 c.c. hydrogen peroxide. This gives no colour change. Blood causes a green or blue colour to appear in three minutes.

Microscopic test.—Blood-corpuscles may be seen after the urine has been centrifuged and the deposit examined. (The most reliable.)

Mucus forms a flocculent cloudiness in the urine, insoluble in acetic acid, soluble in potash. A small amount occurs normally.

Pus occurs in the urine as the result of suppuration in any part of the urinary tract. It forms a white sediment resembling that of phosphates, and, indeed, is often mixed with phosphates. The pus-corpuscles may, however, be seen with the microscope; their nuclei are rendered evident by treatment with 1 per cent. acetic acid, and the pus-corpuscles are seen to resemble white blood-corpuscles, which, in fact, they are in origin. They dissolve in glacial acetic acid.

Some of the protein constituents of the pus-cells—and the same is true for blood—pass into solution in the urine, so that the urine pipetted off from the surface of the deposit gives the tests for protein.

On the addition of liquor potassæ to the deposit of pus-cells a ropy gelatinous mass is obtained. This is distinctive. Mucus treated in the same way is dissolved.

Amino-Acids.—Normal urine contains traces of glycine. Leucine, tyrosine, and other amino-acids may be present after extensive disintegration of tissue protein, such as occurs in acute atrophy of the liver. In the latter condition urea is almost absent from the urine and there is a considerable increase in the ammonia. The amino-acids in such circumstances escape further decomposition and pass unchanged into the urine. Cystine may occur as a rare anomaly of metabolism. Associated with cystinuria one often finds diaminuria, that is, the passage of diamines into the urine; these are known as cadaverine ($C_5H_{14}N_2$) and putrescine ($C_4H_{12}N_2$), and are the result of the removal of CO_2 from the diamino-acids lysine and ornithine respectively.

CHAPTER XXXVIII

THE URINE (*continued*)

Estimations

Total Nitrogen.—Kjeldahl's method of estimating nitrogen consists in boiling the material under investigation with strong sulphuric acid. The nitrogen is thus converted into ammonium sulphate. Excess of soda is then added, and the ammonia distilled over into a known volume of standard acid. The amount of diminution of acidity in the standard enables one to calculate the amount of ammonia, and thence the amount of nitrogen.

Urea.—By the more accurate *urease method* the urea is decomposed into ammonia and carbonic acid by means of the enzyme urease of the soya-bean. The ammonia is then estimated as indicated below; but as the urine always contains a little preformed ammonia, this has to be previously estimated and deducted from the total. The *hypobromite method* is most convenient. If the experiment is performed as directed below, nitrogen is the only gas which comes off, the carbon dioxide which is also formed being absorbed by the excess of soda.

Dupré's apparatus (fig. 181) consists of a bottle (A) united to a measuring tube by india-rubber tubing. The measuring tube (C) is placed within a cylinder of water (D), and can be raised and lowered at will. Measure 25 c.c. of alkaline solution of sodium hypobromite (made by mixing 2 c.c. of bromine with 23 c.c. of a 40 per cent. solution of caustic soda) into the bottle A. Measure 5 c.c. of urine into a small tube (B), and lower it carefully, so that no urine spills, into the bottle. Close the bottle securely with a stopper perforated by a glass tube; this glass tube (the bulb blown on this tube prevents froth from passing into the rest of the apparatus) is connected to the measuring tube by india-rubber tubing and a T-piece. The third limb of the T-piece is closed by a piece of india-rubber tubing and a pinch-cock, seen at the top of the figure. Open the pinch-cock and lower the measuring tube until the surface of the water with which the outer cylinder is filled is at the zero point of the graduation. Close the clip, and raise the measuring tube to ascertain if the apparatus is air-tight. Then lower it again. Tilt

the bottle A so as to upset the urine, and shake well for a minute or so. During this time there is an evolution of gas. Then immerse the bottle in a large beaker containing water of the same temperature as that in the cylinder. After two or three minutes raise the measuring tube until the surfaces of the water inside and outside it are at the same level. Read off the amount of gas (nitrogen) evolved. 354.0 c.c. of nitrogen are yielded by 1.0 gram of urea. From this the quantity of urea in the 5 c.c. of urine and the percentage of urea can be calculated. If the total urea passed in the twenty-four hours is to be ascertained, the twenty-four hours' urine must be carefully measured and thoroughly mixed. A sample is taken from the total for analysis, and thus the total amount of urea is ascertained.

Blood Urea.—In clinical work it is frequently necessary to compare the concentrations of urea in blood and urine. The blood, after removal of the proteins, is treated with soya-bean meal (containing urease) in an acid phosphate solution; the urease converts the urea, but none of the other nitrogenous constituents of the blood, into ammonium carbonate. The solution is then rendered alkaline with potassium carbonate and the ammonia drawn off by suction into a measured amount of standard acid. Subsequent titration of the acid indicates the amount already neutralised by the ammonia liberated from urea, thus the percentage of urea can be calculated. Normally this varies from about 20 mgms. per cent. in young people to 40 or 50 in older persons.

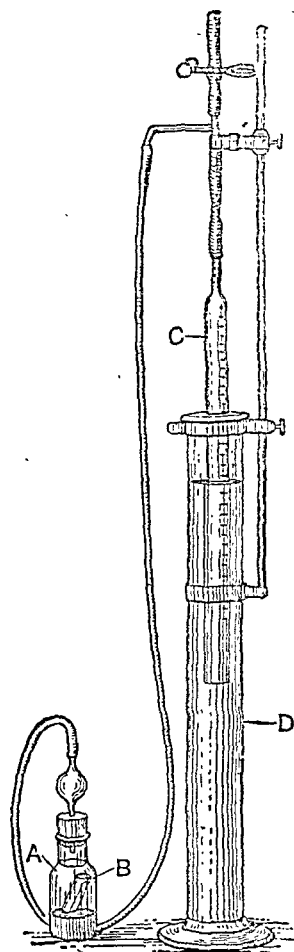


FIG. 181.—Dupré's urea apparatus.

Ammonia — *Sørensen's Method.* — When neutral solutions of ammonium salts are treated with an excess of formaldehyde, the compound hexamethylene tetramine (urotropine) is formed, with the liberation from the ammonium salt of a corresponding amount of acid ($4\text{NH}_4\text{Cl} + 6\text{CH}_2\text{O} = \text{N}_4(\text{CH}_2)_6 + 6\text{H}_2\text{O} + 4\text{HCl}$) which can be titrated in the usual way. The formaldehyde method gives fairly accurate results. Urine (60 c.c.) is stirred with basic lead acetate (3 gms.) (to remove nitrogenous compounds which interfere with the subsequent reaction) and filtered; potassium oxalate (2 gms.) is added to the filtrate which is again stirred and filtered. The clear

filtrate (10 c.c.) is diluted with distilled water (50 c.c.) and a few drops of phenolphthalein (1 per cent.) and potassium oxalate (5 gms.) added. The mixture, if acid, is neutralised with $\frac{N}{10}$ NaOH.

Neutralised formalin (20 c.c. of 20 per cent.) is finally added. The acid thus liberated according to the above equation is then titrated with $\frac{N}{10}$ NaOH. Each c.c. of $\frac{N}{10}$ NaOH used to restore the pink colour corresponds to 0.0017 gm. NH_3 .

Aeration (Van Slyke).—This gives more accurate results than the formaldehyde method. The urine is made strongly alkaline with potassium carbonate which decomposes the ammonium salts. The liberated ammonia is drawn by suction into a measured amount of standard acid. The excess acid not required for neutralising the ammonia is estimated by titration and this subtracted from the original quantity of acid gives the amount equivalent to the ammonia.

Sugar.—The estimation depends on the power of monosaccharides in virtue of their free CHO group to reduce cupric hydrate in alkaline solution to cuprous oxide.

Fehling's solution consists of (1) copper sulphate dissolved in distilled water; (2) Rochelle salt* dissolved in dilute solution of caustic soda. The two solutions are mixed and diluted to a litre.

Benedict's solution, which is now generally preferred, is a similar alkaline solution of copper sulphate containing potassium thiocyanate, which forms a white precipitate with the cuprous oxide formed so that the latter does not obscure the blue colour of the sulphate. It is usually made up so that 25 c.c. of the solution are reduced by 0.05 gm. glucose.

10 c.c. of Fehling's or 25 c.c. of Benedict's solution are diluted and boiled in a porcelain basin. Into this the urine is run from a burette until the blue colour of the copper sulphate disappears. From the amount of urine used the percentage of sugar contained is calculated. If over 1 per cent. is found, the urine is diluted five or ten times and the procedure repeated.

* The Rochelle salt (and sodium citrate in the case of Benedict's solution) keeps the copper in solution.

CHAPTER XXXIX

THE CONSTANCY OF THE INTERNAL ENVIRONMENT

THE necessity for the maintenance of a constancy of the internal environment was first appreciated by Claude Bernard, who referred to it as "*La fixité du milieu intérieur*," which he pointed out is the condition of free and independent life. The general problem of what may be called homeostasis is well discussed by Cannon, 1929.

For practical purposes this means that every living cell must, in order to preserve its normal activity, be surrounded by a fluid with certain physical and chemical characteristics, capable of supplying it with nourishment and with oxygen, and at the same time permitting the products of its metabolism to escape from it. In the case of the single-celled organism, the external environment fulfils these latter requirements, but the environment of the more highly evolved organisms is so complicated and variable that very special mechanisms have become necessary to provide for each cell in the body its suitable environment. Each cell is bathed in lymph or tissue fluid which is more or less in equilibrium with the blood and for practical purposes, therefore, we may in this connection consider the various processes which maintain constant the composition of that fluid. The so-called *blood constants* are not absolute, but are the limits of its variability beyond which the usual function of the cells it supplies is impossible.

In order to maintain any constituent of the blood constant, it is necessary either to have an unlimited immediate supply from the external environment or to have accessible storage in the body which can be released on demand. The storage may be localised in certain regions of the body or generalised and must be replenished from time to time if its amount becomes reduced. In some cases an overflow mechanism is provided should the charging become excessive and a fine adjustment is provided in regard to excretion. Usually the latter is supplied by the selective powers of the body of the kidney tubules to reabsorb substances required by the cells.

Water and Water Balance.

Students reading this section should familiarise themselves with the physico-chemical principles governing the passage of fluids through membranes (p. 291).

Water is essential for all bodily processes and particularly for the transfer of substances from one part of the body to another. It is present normally as "free water" in which a large variety of salts are dissolved, but some may be "bound water" as part of, or attached to, protein molecules where it is less generally available.

The amount of water is approximately constant in the blood and tissues of the body. This is about 70 per cent. of the soft tissues generally, but the exact figure depends on the power of the body to hold water, the amount of water taken in and the amount excreted. Normally the need of the body for water is indicated by the thirst, provided concentrated substances such as salt, sugar, or alcohol have not dehydrated the nerve-endings of the tongue (see Thirst).

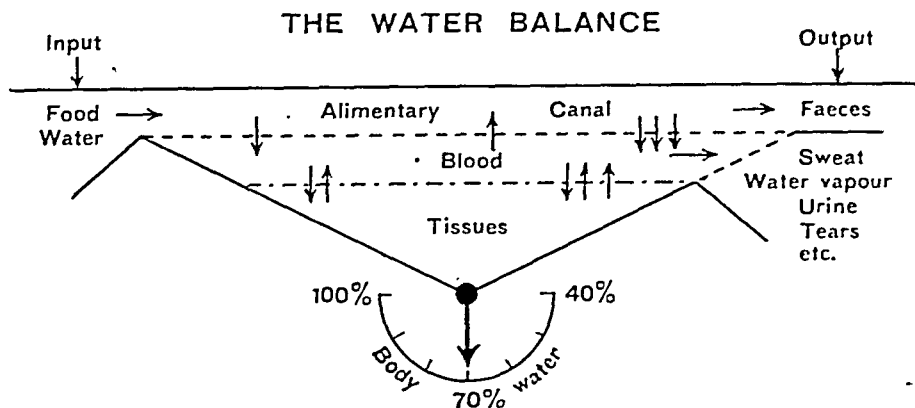


FIG. 182.—The dotted lines indicate semi-permeable membranes.

The source of the water of the body is the diet, not only the water we take as such or in various beverages, but that which is an essential constituent of articles of food, such as green vegetables (over 90 per cent.), fruit (over 85 per cent.), and meat (over 50 per cent.).

In addition we manufacture water by the oxidation of the hydrogen in most dry foods, such as carbohydrates or fats. The volume of oxygen taken in in excess of CO_2 given out is that used in the oxidation of the hydrogen of fats, but much more water is produced in the oxidation of the hydrogen of the carbohydrate molecule for more carbohydrate than fat is normally used. Water is also released in other chemical reactions, such as the building-up of condensation products. Of the total excreted about 40 per cent. is produced in these ways. It is calculated that an ordinary mixed diet of about 3000 calories produces about 300 c.c. of water.

Water loss occurs from the skin, the respiratory tract, the faeces, and the kidney. On occasions it may also be lost in expectoration,

tears, hæmorrhage, etc. Normally the water loss is balanced by the intake and that manufactured from foods. (See fig. 182.)

Excessive water loss is prevented automatically by the increased concentration of the blood, raising its osmotic pressure so that capillary pressure and thereby the production of urine and sweat is counteracted. If, for example, there is excessive sweating it eventually stops, but this may be followed by profuse perspiration a few minutes later after taking a glass of cold water.

The kidney, which excretes three times as much water as the skin or respiratory tract, may be looked upon as the fine adjustment of water loss, for in virtue of its glomerular membrane it responds most readily to the concentration of the blood and the blood-pressure. If excessive water is lost by any other route of excretion the water loss by the kidney is reduced. Thus excessive sweating, vomiting, or diarrhoea causes a reduction in the amount of urine. The amount lost by the respiratory tract varies in different animals. Those which do not sweat excrete larger quantities by the respiratory tract as is suggested by the panting—rapid shallow respiration—of dogs and sheep on hot days.

If there is excessive loss compared with intake for a prolonged time the reduced blood volume and fall of capillary pressure leads to a withdrawal of fluid from the tissues, the skin becoming obviously shrunken in appearance. The amount of water lost is determined roughly by the amount taken in, but if salt is taken in at the same time it may be held in the body temporarily until the salt is excreted. Thus if 1000 c.c. of additional water is drunk it is excreted in about three hours, but if this amount of a solution of sodium chloride or sodium bicarbonate is taken the excretion may be delayed for forty-eight hours. (See Adolph, 1923.) Food, likewise, may hold up the absorption and excretion of ingested water. Other salts, such as magnesium sulphate, are either not wholly absorbed from the alimentary canal or are excreted more rapidly by acting as diuretics. Calcium salts reduce the power of the tissues to hold water.

The ingestion by the mouth or even the intravenous injection of isotonic salt solution produces, however, a very transient effect on the blood volume, the additional fluid rapidly passing into the tissues because of the increased capillary pressure and reduced osmotic pressure it tends to produce. In excess it tends to accumulate in the serous cavities and the muscles.

If the water loss has been accompanied by excessive loss of salts, as in the case of sweating, the taking of water to replace that lost is not sufficient; indeed, it may actually so aggravate the condition by promoting sweating that the unconsciousness which occurs is called "water intoxication," a term introduced in hot

mines in America where this condition is liable to occur. Sodium chloride seems to be the chief salt concerned and is discussed below.

The activity of the kidney is determined by the permeability of the capillary walls of its glomeruli and tubules; indeed, it is the histology of the capillary walls generally which may be looked upon as determining the osmotic pressure of the blood and the blood-pressure. (Peters, 1935; Mariott, 1923; McLean, 1925; Rowntree, 1922; Starling, 1909; Van Slyke, 1926.)

Sodium Chloride.—Although in the blood the content of sodium chloride remains constant, the mechanisms by which it is brought about are by no means clear. It is known that the sodium and chloride content may vary independently and it is probable that we may consider the sodium as part of the general alkali reserve. It is necessary, as we have seen, for the maintenance of the heart-beat, and its salts assist materially in maintaining osmotic relationships generally. (See Macallum, 1926.)

Sodium chloride is stored particularly in the skin, whence it may be drawn if the salt intake is deficient. The storage becomes apparent in sodium chloride deprivation, when the skin content is materially reduced. When then a known amount is administered there is a considerable retention even if a water diuresis is produced (Baird and Haldane). It has also been shown that the chloride content of the blood varies inversely with the carbon dioxide content (Christy).

The retention of sodium chloride is profoundly affected by removal of the adrenal cortex probably because its hormone is intimately concerned with the maintenance of capillary permeability. Excessive loss of chlorides may occur from excessive sweating and leads to "miners' cramp" and even to unconsciousness and death. In hot mines and in hot desert climates man and animals both find it beneficial to drink salines. Excess salt loss may occur from continuous vomiting or when large quantities of ascitic fluid are frequently removed from the abdominal cavity. Excessive fatigue and general exhaustion are usual symptoms (McCance). There may be a marked loss of weight and impaired kidney function.

Sodium is the chief metallic ion of the body fluids as its salts are freely soluble, but it does not permeate membranes easily. If the heart or muscles are deprived of sodium they cease to be excitable.

Potassium Chloride.—*Potassium* exists in free ionic form in all plants in which it is necessary for the formation and function of the green pigment chlorophyll. Deprived of it plants will not grow. In animals it is the natural antagonist to calcium for the blood maintains a Ca/K balance. Young rats deprived of potassium will not grow. It is the most radio-active element in the body. It is

the chief metallic ion *inside* cells and is released in nerve tissues when they conduct impulses (Vanhems, 1934). The potassium must, however, always be proportional to the calcium of the blood (as has been seen in relation to the heart-beat). Its storage is seen by its rapid disappearance from the blood if injected intravenously, while it reappears from the liver on sympathetic or adrenaline stimulation (D'Silva), but otherwise nothing is known regarding its control. A high intake of potassium salts increases the excretion of sodium salts.

Calcium Salts.—Calcium is probably necessary for the proper activity of every living cell. It is necessary for the contraction of all muscles, including that of the heart, for the clotting of blood and of milk, for the action of some enzymes, and for the formation of bone. Calcium is commonly precipitated in the region of chronic irritation or infection, *e.g.* in infected glands. It is also laid down in diseased blood-vessels which may become quite rigid and brittle like pipe-stems. The **blood calcium** is maintained at about 10 mgs. per 100 c.c. of serum and exists in three forms. About 45 per cent. of this is non-diffusible and in organic combination, and of the diffusible 35 per cent. is ionized. We can say, therefore, that the active blood calcium is only about one-fifth of the whole.

Calcium is absorbed from the food since in neutral or alkaline solution the calcium salts are precipitated especially as carbonates and phosphates. Some biochemists hold that absorption takes place chiefly in the jejunum where the reaction is most acid and is greatly facilitated by fats and lactose which produce fatty acids and lactic acid; but it is doubtful if the jejunum is acid in the *living* animal.* Its absorption probably depends more on bile salts, amino-acids and vitamin D, as stated on p. 374. Calcium is stored in the bones. Birds, under the influence of their sex hormones grow special bone in the medullary cavities of their long bones as a calcium storehouse to be drawn upon for egg-shells just as mammals draw upon bone calcium stores for milk. If absorption is inadequate, faulty ossification of the bones takes place. (See Vitamin D and Rickets.) Calcium is excreted by the large intestine and kidney, but little is known about its excretion. In the maintenance of the blood calcium constant the parathyroid glands play an important rôle.

There is increasing evidence from experimental work on isolated tissues that the calcium-potassium balance in the blood is of the utmost importance, and although no diseases have as yet been shown clearly to be due to an imbalance it seems most probable that it will one day have a more practical significance. (See Hunter and Hess, 1929.)

* Killing or anæsthetisation of the animal relaxes the pylorus and allows acid through.

The Parathyroid Glands.

These are small bodies, usually four in number, situated near or embedded in the substance of the thyroid. They are made up of elongated groups of polyhedral cells, bound together by connective tissue, and well supplied with blood-vessels. In addition to these *chief cells*, *eosinophile* cells are found in small numbers. Some have supposed that parathyroid is only immature thyroid tissue, but a study of development shows that the parathyroids have a different embryonic origin from the thyroid, and in the lower vertebrates the two organs are entirely distinct. Most of the facts concerning the thyroid were discovered previous to the recognition of the parathyroids, and it has gradually become evident that in removing the thyroid it was really the simultaneous removal of the parathyroids which caused the nervous symptoms. The most prominent signs after extirpation of the parathyroids are those of tetany (muscular spasms and twitchings).

When Schiff removed the thyroid gland in dogs he found that some did not die for some time, but others died in convulsions after a few days. Later work showed that in the animals and human beings which died rapidly after operation the loss of the parathyroid glands was really responsible. To-day when the thyroid is removed in the treatment of goitre two parathyroids are left with the lower poles of the gland.

In 1909 MacCallum and Voegtlin found that in tetany there was a reduction of the blood calcium, but it was not until Collip prepared an active extract in 1925 that the relationship was accepted. An animal in which the parathyroids are removed is convulsive, has an excessively rapid heart, and would die from exhaustion within forty-eight hours; but it may, by the injection of the extract, be kept alive. Further, the blood calcium, which may have fallen to about half the normal 10 mgr. per 100 c.c. of blood, will rise, possibly well above normal. As the blood calcium rises there is a corresponding fall of blood phosphorus.

On the other hand, it is found that if excessive parathyroid is administered the blood calcium may become double the normal, and instead of there being the hyperexcitability seen above, there is a general depression of the nervous system with drowsiness, muscular flaccidity and unconsciousness, which results in death. Clotting of the blood occurs in the vessels immediately after death.

Glandular tumours of the parathyroid have now been described in man. Such subjects show softening of the bones as a result of increased calcium mobilisation, but the condition is now recognisable before the nervous symptoms appear.

An excessive loss of calcium occurs in the female when pregnant

or lactating, and if the diet is deficient in calcium the serious condition of osteomalacia which is associated with generalised softening of the bones may occur. The disease is seen not infrequently in China and India. In cows after calving the similar but rapidly fatal disease of "milk fever" was seen commonly in Britain. The recovery of the animal almost at the point of death if calcium is administered as calcium gluconate, or if air is injected into the udder to prevent calcium excretion, is dramatic.

There is, however, considerable doubt as to how parathyroid acts. It may affect the osteoclastic cells of bones directly, but it may act indirectly by an action on the kidneys. The latest work appears to support this view. For example, the rise of blood calcium produced by parathyroid extract is prevented by removal of the kidneys, tying the ureters or the renal vessels. The rise of blood calcium is also prevented by administering acid sodium phosphate at a rate which prevents the fall of blood phosphorus which would occur. This latter observation suggests that the action of the parathyroid may be primarily on the phosphorus excreting mechanism of the kidney. (Collip and Neufeld.)

We must understand that in the regulation of calcium metabolism the parathyroid co-operates with other agencies, *e.g.*, with the vitamin D of the diet, which influences calcium retention in the body.

It has also been shown that the hormone of the parathyroid has the power of retarding the growth of young animals (Collip), but how this is brought about is unknown. It has been suggested that this action is distinct from an effect on the blood calcium, but this is uncertain.

In addition to the above function, considerable evidence has been put forward by Noel Paton and by Burns that the parathyroid is also concerned with the protection of the body against the substance guanidine, which is closely related to the creatine of muscle or methyl-guanidine acetic acid. How this fact may be related to the other activities of the gland is unknown.

Phosphorus.

This account of the rôle of phosphorus in the body is given in summarised form, as details are discussed elsewhere in appropriate sections.

Phosphorus is essential for all organic life and occurs in the blood of man to the extent of 24 to 52 mgs. per 100 c.c. The organic phosphorus occurs for the most part in the plasma as glycerophosphate, hexosephosphate and nucleotides; the phospholipides are in the corpuscles. The inorganic phosphates may be half the normal (4 to 6 mgs.) in rickets, but if we may judge from

the common occurrence of phosphates in tonic medicines, phosphorus deficiency is common, especially after infection.

The actual level of the blood phosphorus appears to depend on the activity of the parathyroid gland (see above). It varies inversely as the calcium. It falls when parathyroid extract or insulin is injected.

Phosphorus is concerned:

1. In the formation of bone and teeth.
2. In the formation of many organic substances, phosphoproteins, nucleic acid, phospholipides, creatine phosphate, adenylyl pyrophosphate and the like.

3. In the buffering of the blood and other body fluids.

4. In the transport of fat and lipides.

5. In the chemistry of muscle contraction. It appears to be specially important in the breakdown of glycogen (see *Chemical Changes in Muscle*) for which phosphorylation, i.e. the adding of phosphoric acid, is essential.

6. In the activities of the alimentary canal. Phosphates, if injected intravenously or if applied to isolated gut in Ringer's solution, exercise a marked stimulating action on intestinal movements. For some unexplained reason the administration is of great value in the treatment of intestinal flatulence.

It is excreted chiefly in the urine in combination with sodium, potassium, magnesium and ammonium, the actual salt depending on the reaction of the urine. (See *Urine*.)

About a third is excreted in the fæces according to the necessity to get rid of alkali and undigested organic phosphorus.

Glucose is necessary as a fuel and provides almost a complete example of the principle of constancy of internal environment. It is stored particularly in the muscles and in the liver. The further needs of the muscles are met by use of the store in the liver which is replenished from the diet. Hunger probably represents the call of the body for carbohydrate (Lawrence), but no doubt the sensation has become vitiated. The liberation of the liver glycogen is brought about by the secretion of adrenaline and probably by nervous stimulation, and the storage in the muscles and in the liver by the action of insulin. If the liver glycogen gets used up, as in starvation, protein and fat provide the necessary fuel. The subject has been discussed at length under *Metabolism of Carbohydrates*.

Fat and Amino-Acids are dealt with in the sections on *Fat Metabolism* and *Protein Metabolism*, but as yet we have little information as to how the constancy of the blood composition in regard to them is maintained.

Body Temperature.—See separate chapter.

Hydrogen-ion Concentration.—See separate chapter on the Acid-base Equilibrium of the Body.

Blood Gases.—These have been dealt with in relation to respiration. As the supply of oxygen and carbon dioxide is normally unlimited, no storage is necessary—the more so as carbon dioxide can be replaced in the blood to some extent by chlorides. The storage of oxygen which occurs in foodstuffs is negligible, since the body at rest requires about 300 c.c. per minute. Excessive excretion or accumulation of carbon dioxide is prevented by the chemical control of the respiration.

Hormones.—Probably the products of the ductless glands which have a continuous action are present in the blood in minimal amounts which may be greatly increased from time to time, but the exact mechanisms concerned are in most instances not understood.

The Natural Mineral Appetite.

A most remarkable fact is that animals apparently develop a craving for minerals deficient in the diet. Rats prefer calcium solutions to water if deprived of calcium, especially after parathyroidectomy. In some areas short of minerals animals develop diseases due to the eating of skeletons, and in moorland areas animals welcome "salt licks." In the campaign in Sinai, 1915-17, horses and uninstructed men were found to prefer brackish water to fresh. Evidence on these points is accumulating.

CHAPTER XL

THE ACID-BASE EQUILIBRIUM OF THE BODY

The Reaction of Fluids

WHEN hydrochloric acid is added to water, the water becomes acid because the HCl dissociates into its component ions of hydrogen and chlorine. If a more complex acid such as acetic is used, its hydrogen forms one ion and the remainder of the acid another. The acidity or alkalinity as determined by titration in the ordinary way gives not only the dissociated but also the undissociated acid and therefore gives little information regarding the activity of the solution. The real strength or degree of acidity depends on the number of hydrogen-ions present in the solution. HCl is a strong acid because the dissociation is nearly complete; lactic acid is a weak acid because the number of free H-ions is less, and their concentration does not rise proportionally to the amount of lactic acid present.

In the same way the degree of alkalinity of a solution depends on the concentration of hydroxyl (OH)-ions. But in any solution if the concentration of H-ions is multiplied by that of OH-ions the product is constant.

In a solution which turns blue litmus red, the H-ions preponderate but OH-ions are not absent; in a solution which turns red litmus blue the reverse is the case.

Pure distilled water dissociates to a trifling extent into H and OH-ions which of necessity are equal in number and we call water neutral, not because it is neither acid nor alkaline but because it is both in equal degree. Lactic acid is a weak acid because it undergoes less dissociation than, say, HCl.

Hydrogen-ion Concentration.—Now since it can be shown that in any solution the product of the concentration of H-ions multiplied by the concentration of OH-ions is constant, the concentration of hydrogen-ions in a solution may be used to express either acidity or alkalinity. In pure water it has been determined by experiment that the concentration of hydrogen-ions, *i.e.* the *cH* per litre is 0.0000001, $\frac{1}{10,000,000}$ gram, or $\frac{1}{10^7}$, or as it is more commonly expressed, 10^{-7} .

The H-ion concentration of the blood is almost inconceivably small, being only 0.000000032 or one gram-ion in 32 million litres. Small as this number is, slight variations in it produce profound physiological disturbance; if, for instance, the figure in arterial blood rose to 0.000000034 breathing would be appreciably affected, and if it rose to 0.00000005 the person would be hopelessly out of breath.

pH.—For convenience the numerical value of the power only is used; water is thus described as having a pH (power of hydrogen) of 7. Since this is neutrality, acid solutions have a pH ranging from 0 to 7 and alkaline solutions vary from pH 7 to 14. Hence, as pH increases the acidity or hydrogen-ion concentration decreases and *vice versa*.

It is to be noted that the pH scale is a logarithmic one and therefore a change of pH from 6 to 7 represents a much larger change in hydrogen-ion concentration than does a change from 7 to 8.

The Determination of the pH of physiological fluids is usually carried out by the colorimetric method in which advantage is taken of the fact that certain dyes change their tint according to the hydrogen-ion concentration of the fluids in which they are dissolved. Thus, for example, phenol red goes through a series of changes from yellow to red between pH 6.8 and 8.4. Different indicators have different ranges and neutral points. The old-fashioned litmus changes from blue to red at about 6.6. Congo red, on the other hand, changes from red to blue at about 4, hence its value in distinguishing between HCl of the gastric juice and the less dissociated organic acids such as lactic and butyric. In making the determination the indicator is added to the unknown fluid and the colour compared with a series of standards of which the pH is known. The indicator method, although very accurate for most purposes, is liable to be inaccurate in the presence of protein and salts. In determining the pH of blood, therefore, certain special procedures must be carried out (see p. 558).

Electrical Method.—This is really the original method and consists in determining the electromotive force set up between a hydrogen electrode and the free hydrogen-ions in solution. The method is still used when the indicator method is unsuitable and for checking standard solutions made up in the ordinary way.

The Reaction of the Blood.

Blood is a fluid which is alkaline to litmus. It contains H-ions but they are overbalanced by OH-ions. The principal acid to which this hydrogen-ion concentration is due is carbonic acid (H_2CO_3), and if carbonic acid gas (CO_2) is passed into water, or

a physiological saline solution, in increasing amount, the concentration of hydrogen-ions increases also. Carbonic acid is continually being thrust into the blood by the tissues, and the reaction is but little disturbed because of the mechanisms which exist for its transport. The maintenance of the acid-base equilibrium in the blood is most important. The various cells and tissues it nourishes demand a reaction which is almost neutral, and perhaps there is no other collection of cells which are so sensitive to variations from the normal as those which make up the respiratory centre; the figures already given show how a very slight increase in the hydrogen-ion concentration of the blood stimulates them to excessive action, and produces exaggerated breathing (hyperpnœa).

We have now to consider the way in which the normal acid-base relationship is maintained, and to discuss more fully the effects which ensue when this balance is upset. In relation to the transport of CO_2 by the blood we saw that the majority of it became sodium bicarbonate and a small quantity of it remained in free solution in the plasma. Both these substances can readily be got rid of according to the requirement of the body. For practical purposes therefore it is convenient to consider that, although there are a multitude of substances in the plasma, only two need be taken into account. One of these, CO_2 , when dissolved in water is *acid* (H_2CO_3); the other, sodium bicarbonate (NaHCO_3), is *alkaline*. The way in which the relative concentrations of these two substances affect the hydrogen-ion concentration of the blood is quite simple, viz., that the hydrogen-ion concentration varies directly with the ratio (normally $\frac{1}{20}$) of the one substance to the other. For convenience it has been agreed that the words "concentration of" shall be expressed by square brackets and hydrogen-ion by H^+ . Concentration of hydrogen-ions is thus abbreviated to $[\text{H}^+]$, and this as

stated above varies as $\frac{[\text{H}_2\text{CO}_3]}{[\text{NaHCO}_3]}$ or what comes to the same thing

$$[\text{H}^+] = \frac{k[\text{H}_2\text{CO}_3]}{[\text{NaHCO}_3]}, \quad k \text{ being a constant.}$$

In relation to acidæmia and alkalæmia below, we shall see that the body has many mechanisms by which this ratio is kept constant.

The reaction of the blood may conveniently be determined by the **method of Dale and Evans**, which consists essentially of placing the blood in a small dialysing bag inside a small tube of physiological saline and subsequently, when dialysis has taken place, determining the $[\text{H}^+]$ of the saline. Or the blood may be centrifuged and the $[\text{H}^+]$ of the plasma, diluted, taken.

In each case the blood is kept under oil to prevent loss of CO_2 . Oxalate is added to prevent clotting and fluoride to prevent glycolysis.

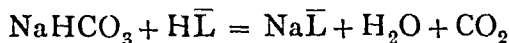
The $[H^+]$ is determined colorimetrically by comparing the colour of the fluid with salines or diluted plasmas respectively of known H-ion concentration to which indicators have been added.

The reaction is normally about pH 7.4, but life is possible with a much more alkaline blood. Death however occurs if the blood becomes acid to a very slight degree. We shall see however below that the body is well provided with mechanisms to prevent this occurring.

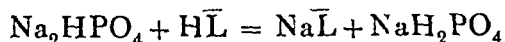
Acidæmia.

In acidæmia there is a tendency of the blood to become acid.

This occurs, physiologically, in muscular exercise when large quantities not only of carbon dioxide but also of lactic acid are thrown into the circulation. The lactic acid is dealt with in several ways and in disease the body deals with other acids similarly. First there are the "Buffer Substances," which are so called because they "soak up" the acid, so to speak. They are the sodium bicarbonate and the alkaline sodium phosphate of the blood, which react with acid thus—



[Sodium bicarbonate+lactic acid.] = [Sodium lactate+water+carbon dioxide.]



[Alkaline sodium phosphate+lactic acid] = [Sodium lactate+acid sodium phosphate.]

The carbon dioxide formed from the bicarbonate stimulates respiration and is excreted by the lungs and the acid sodium phosphate is excreted by the kidney. The reaction of the blood, therefore, remains practically unchanged since the substances formed are little dissociated and are rapidly got rid of.

The hæmoglobin proteins of the blood also take up acid since they are amphoteric. It should be noted that the buffering power of these various constituents is by no means equal. The relative values of the different buffers may be represented by the figures: bicarbonate 64 per cent., hæmoglobin 29 per cent., plasma proteins and phosphates, 7 per cent.

The Alkali Reserve of the Body.—We have seen in relation to the carriage of carbon dioxide that the alkali available in the blood itself for the transport of this and other acids is known as the *alkali reserve of the blood*, but it is now evident that this alkali by no means exhausts the resources of the body in this respect. (See Transport of Carbon Dioxide.)

In addition, the body makes use of the ammonia which, as we have seen, appears as a product of protein metabolism. This function appears to be carried out by the kidney, which has the power of breaking down urea and of utilising the ammonia so formed

to neutralise acid. The evidence that the kidney does this is that the renal vein may contain more ammonia than the artery and in renal disease, although an acidæmia may be present, the ammonia-urea ratio is unaltered (McLean). In severe exercise there is, then, an increased excretion of ammonium salts, with a corresponding diminution in the urea content of the urine. The latter becomes more acid because, as we have seen, of the increased excretion of the acid sodium phosphate. These facts, together with the fall of the alveolar CO_2 which results from the stimulation of the respiratory centre, have an important clinical significance, as they may be taken as evidence of the presence of abnormal acids in the blood, such as may be produced from the faulty oxidation of fats in diabetes.

A mild degree of acidæmia takes place on a meat diet because of the sulphur of protein which requires alkali to convert it into sulphates, and all the characteristic changes in the urine are observed.

Several other mechanisms also assist in maintaining the reaction of the blood. Normally the animal takes in an excess of alkaline phosphates which are excreted by the bowel. In acidæmia, more of this phosphate is retained.

It has been shown also (Christy) that the more CO_2 there is in the blood, the less the chloride; indicating that the tissues have some power to take up acid in an emergency. This chloride may, in part, be excreted by the kidney, but not wholly so, as it may return to the blood if the CO_2 falls. This emphasises the fact that the alkali reserve may be held, quite properly, to refer to the whole body, since every one of its cells is capable of taking up in the same way a small amount of acid in virtue of the buffer substances it contains.

When the body succeeds in thus overcoming the addition of acid without there being any actual rise of the hydrogen-ion concentration of the blood, the acidæmia is said to be *compensated*; but as soon as the compensation fails and the hydrogen-ion concentration of the blood rises, a condition is very soon arrived at which is incompatible with life.

Alkalæmia.

In alkalæmia the blood tends to become more alkaline. Such a condition may be produced when an individual **over-ventilates** voluntarily, or as a result of stimulation of the respiratory centre by heat, *e.g.* a hot bath, or at a high altitude when probably the want of oxygen stimulates the respiratory centre. It is observed, to a small extent, in the early forenoon, when respiratory activity is very great. Clinically it may be the cause of death in cases of prolonged **vomiting** which leads to an excessive loss of hydrochloric

acid from the stomach. In such circumstances we have the opposite state of affairs to that in acidæmia—namely, decreased excretion of ammonia by the kidney and increase of urea, with an alkaline urine due to the excretion of alkaline sodium phosphate. Further, since the H_2CO_3 is reduced, it becomes necessary, in order to keep the ratio $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$ at about $\frac{1}{20}$ th, to excrete bicarbonate by the kidney, which still further contributes to the alkalinity of the urine. There is, then, a diminution of the alkali reserve of the blood, not because of acidæmia, but as a compensation for an alkalæmia (Henderson).

This compensation is an important factor in adaptation to high altitudes where as a result of oxygen-want there is a stimulation of respiration which causes a washing out of carbon dioxide.

A tendency to alkalæmia exists normally when a vegetable diet, which produces largely alkaline substances, is taken and a similar tendency is said to occur when the stomach secretes HCl.

In such circumstances, not only do we get urinary changes, but the respiration is automatically depressed slightly, the alveolar content of the carbon dioxide increases and acid is thereby retained; chlorides also pass into the blood from the tissues (Christy).

In alkalæmia there occurs a diminution in the ionic calcium of the blood with an increase in the un-ionized. Severe degrees of alkalæmia for this reason bring about tetany—*i.e.* spasms of certain muscles, especially of the hands and feet. The facial nerve is commonly hyperirritable to tapping. (See Parathyroid Glands.)

Alkalæmia is important clinically, not only because it may cause death after excessive vomiting, but the alkalinity of the urine causes crystals, notably those of phosphates, to be precipitated and great irritation of the urinary bladder may be caused.

The Hydrogen-ion Concentration of Other Body Fluids.—It seems probable that conditions liable to change the reaction of the blood will change the reaction of all fluids made from the blood. We have already seen this in relation to the urine, but the same probably applies to tears and, what is of more importance, to digestive secretions. This is certainly true of saliva, which may change its reaction very appreciably (Mathur) in response to diet and other conditions.

CHAPTER XLI

THE FUNCTIONS OF THE SKIN

Protection.—The protection depends on the epidermis, that is, thick layers of epithelial cells which become flattened and even horny in those areas such as the soles of the feet where there is much hard wear. The superficial layers are constantly being replaced by the growth of the cells in the deeper layers which gradually flatten as they approach the surface. In the process some of the protoplasm of the cells becomes transformed into granular eleidin which characterises the stratum granulosum, but gradually the cells clear to form the stratum lucidum until the keratin of the horny surface layer is formed. The nails are thickenings of the stratum lucidum.

The protection afforded by the skin is still further enhanced by its movement on the underlying structures which causes blows to glance off.

In regard to the body as a whole the skin gives even more protection by its possession of nerve-endings, stimulation of which gives rise to protective movements. In some animals sensation is increased by the possession of hairs (*e.g.* whiskers of cats) with specialised receptors at their bases. (See Danforth, 1939.)

Heat Regulation.—See chapter on Body Temperature.

Respiration.—A small amount of respiratory interchange of gases occurs through the skin, but in thick-skinned animals this is very small. In man, the carbonic acid exhaled by the skin is about $\frac{1}{150}$ to $\frac{1}{200}$ of that which passes from the lungs. But in thin-skinned animals, such as frogs, cutaneous respiration is very important; after the removal of the lungs of a frog, the respiratory interchange through the skin is sufficient to keep the animal alive, the amount of carbonic acid discharged being about half as much as when the lungs are present (Bischoff).

Absorption.—This also is an unimportant function; but the skin will in a small measure absorb oily materials placed in contact with it; thus many ointments are absorbed, and general effects are produced by inunction of substances dissolved in animal fats.*

* Many alleged cases of poisoning through the skin are really due to minute quantities being taken in by the nose or mouth.

Secretion.—The secretions of the skin are two in number. The *sebum* is the natural lubricant of the hairs. The secretion of *sweat* is an important function of the skin, and we will therefore discuss it at greater length.

Blood Depot.—The skin also functions as an important store-house of blood, which is called upon whenever blood is needed in the muscles or other organs. Thus, pallor of the skin is produced, and the subject looks pale in a variety of states such as hæmorrhage, cold, anger, fear, and infections, which bring about sympathetic stimulation as a compensatory mechanism. When the blood is withdrawn from the skin its temperature falls and the subject may feel chilly.

The blood is stored in the rich vascular sub-papillary plexuses of the dermis or true skin. It has been estimated by Barcroft that the skin of an adult may hold about a litre of blood.

THE SWEAT.

The Secretion of Sweat.—The sweat-glands are most abundant in man on the palms and soles, and here the greatest amount of perspiration occurs. Different animals vary a good deal in the amount of sweat they secrete, and in the place where the secretion is most abundant. Thus the ox perspires less than the horse and sheep; perspiration is absent from rats, rabbits, and goats; pigs perspire mostly on the snout; dogs and cats on the pads of the feet only.

The glands which produce it lie in the deeper layers of the skin and have long corkscrew-like ducts which pass through the more superficial layers to the surface. When the sweat glands are studied in more detail they may be divided into two types: (1) the *apocrine* or *large glands* which are derived from the hair follicles and which include the ceruminous glands of the ear, those of the eyelid, and the mammary glands. The change of the mammary gland from a sweat gland to one which produces milk is an interesting study in evolution; (2) the small or *eccrine glands* which are derived from the epidermis and scattered all over the body. The distribution of the large glands varies very much from individual to individual and from race to race. They are said to be in many instances of sexual significance and to become less so as we ascend the evolutionary scale. In humans the small sweat glands predominate, and the large glands are restricted to the face, ears, axillae, and the sexual areas.

As long as the sweat is small in amount it is evaporated from the surface at once; this is called *insensible perspiration*. There is, however, some evidence that the insensible perspiration is not secreted but diffused as water vapour through the epithelium,

for it is present in those persons in whom there is a congenital absence of sweat glands. (Kuno, also Whitehouse, Hancock, and Haldane.) As soon as sweating is increased or evaporation prevented, drops appear on the surface of the skin. This is known as *sensible perspiration*. The relation of these two varies with atmospheric conditions; the drier and hotter the air, the greater is the proportion of insensible to sensible perspiration. In round numbers the total amount of sweat secreted by a man is about 450 c.c. in the twenty-four hours, but it may rise to 10,000 c.c. in extremely hot dry atmospheres, especially if there is muscular exercise.

Composition of the Sweat.—Sweat may be obtained in abundant quantities by placing the animal or man in a closed hot-air bath, or from a limb by enclosing it in a vessel made air-tight with an elastic bandage. Thus obtained, it is mixed with epidermal scales and a small quantity of fat-like matter from the sebaceous glands. The continual shedding of epidermal scales is in reality an excretion. Keratin, of which they are chiefly composed, is rich in sulphur, and, consequently, this is one means by which sulphur is removed from the body.

The reaction of sweat is acid, and the acidity, as in the urine, is due to acid sodium phosphate. In profuse sweating, however, the secretion usually becomes alkaline or neutral. It has a peculiar and characteristic odour, which varies in different parts of the body, and is due to volatile fatty acids; its taste is saltish, its specific gravity about 1005.

The percentage of solids is approximately 1·2, of which 0·8 is inorganic matter.

The salts are in kind and relative quantity very like those of the urine; sodium chloride is the most abundant salt. Funke was unable to find any urea, but most other observers agree on the presence of a minute quantity. It appears to become quickly transformed into ammonium carbonate.

In severe muscular exercise the excretion of lactate may be very considerable in the first half hour, but it then falls off (Kuno). This substance appears to be a special excretion of the sweat-glands.

Because of the salt excretion by the skin patients suffering from kidney disease and deficient excretion are usually subjected to hot air baths. It seems doubtful if this is of any appreciable value in view of the small amount in the sweat, but it may be that in kidney disease this excretory function of the skin is increased.

The cerumen is a specialised secretion produced by modified sweat-glands in the external ear.

The sebum is a fatty secretion containing ischolesterol in addition to fat and is produced by glands round the roots of the hairs to which it acts as a lubricant. The open ducts of the glands

are often apparent on the nose. It is the blockage of these glands which gives rise to blackheads and papules, especially in young adolescents. The dried secretion which blocks the ducts may be dissolved out by fat solvents. Sebaceous glands occur in the lips and glans penis independently of hairs. The sebum extracted from sheep's wool is known as lanoline which is much used as a basis of ointments and face creams.

The Control of Sweat Secretion.—There are probably two types of sweat secretion, the hot or thermal sweat and the mental or cold sweat, but whether the mechanisms for them are different has not been determined.

Thermal sweating is generalised and occurs when the body temperature is raised by increased metabolism, commonly that of muscular exercise or when the external temperature is high. It is not present, however, on the palms of the hands and soles of the feet. It is brought about through the operation of the heat-regulating mechanism discussed in the next section.

The application of heat to a part of the body may, however, cause local sweating by direct action on the glands or by a local reflex. Sweating is accompanied by a dilatation of the blood-vessels of the region, presumably the result of the production of metabolic products.

Mental sweat, on the other hand, predominates on the palms and soles, but it is also present in the head and neck and elsewhere. It occurs in many different kinds of emotion, even doing mental arithmetic. It may be produced experimentally (Kuno) by touching any very hot object, such as an electric globe, with the finger for a few seconds. The term mental is held to include that produced by sensory stimulation.

In muscular exercise the sweating is both thermal and mental. Sweating is reduced by cold, which at the same time reduces the cutaneous circulation. It is also reduced by dehydration, whether the result of deprivation of fluid intake or by sweating itself. When the latter occurs, and this is common in hot countries, the taking of a glass of cold water which dilutes the blood produces a profuse sweating.

The exact nervous mechanisms concerned in sweating are not completely understood, and different animals appear to vary appreciably.

The sweat-glands are supplied with sympathetic nerves (Langley), but are peculiar in being stimulated by pilocarpine like other glands and paralysed by atropine. If, for example, the sympathetic nerves supplying the arm are removed surgically, as is not infrequent to relieve spasm of the blood-vessels in the hand (Raynaud's disease), the arm no longer takes part in generalised sweating.

Adrenaline produces profuse sweating in the horse and sheep, but not in man.

Excretion by the Skin.—In addition to the normal constituents of the blood referred to above the skin excretes drugs which may be administered, notably mercury, arsenic, quinine, iodine, while in diseases a vast variety of substances, cystine in cystinurics, glucose in diabetes, albumin in rheumatism, and many others, have been found. (Kuno.)

The Hairs.

In man the hairs appear to be largely vestigial, that is, a relic of our hairy ancestors, but many individuals are much more hirsute than others.

In the lower animal hairs subserve several functions. They materially assist in the conservation of heat and in altering the apparent size of the animal, and in both these functions they may be erected by the small muscles, the *arrectores pilorum*, at their bases.

It seems probable that in man the hair in the flexures acts like a lubricant to reduce friction, and on the head is, like the looseness of the scalp, of advantage in protecting the skull against injury by allowing slip on the cranium.

The Pigment of the Skin.

Pigment becomes deposited in the skin in response to irritation. It is seen particularly in response to light or friction. It occurs in the face and hands to a slight extent, but is marked in the region of the external genital organs and nipples, especially in women who have suckled infants. Pigmented moles are common.

The pigment is melanin which is probably produced from tyrosine (*q.v.*).

Adrenaline is also made from tyrosine (see adrenaline) and in disease of the adrenal glands excessive pigmentation of the skin is usual. It may be that the tyrosine not used for the making of adrenaline is converted into melanin.

The melanin in the skin of the coloured races depends on hereditary factors.

CHAPTER XLII

BODY TEMPERATURE

SINCE departures from the normal body temperature are among the fundamental physical signs of disease, and since observations of the temperature of the patient are only less frequent in medical practice than those of the pulse or of the tongue, it is necessary to have as complete an understanding as possible of the principles that regulate the fluctuations of the clinical thermometer.

Animals may be divided into two great classes:—

(1) Warm-blooded or *homoiothermal* animals are those which have an almost constant temperature. (Mammals and birds.)

(2) Cold-blooded or *poikilothermal* animals are those whose temperature varies with that of the surrounding medium, being always, however, a degree, or a fraction of a degree, above that of the medium. This class includes reptiles, amphibians, fish, embryonic birds and mammals, and probably all invertebrates.

The temperature of a man in health varies but slightly, being between 35.5° and 37.5° C. (97° to 99° F.). Most mammals have approximately the same temperature: horse, donkey, ox, 37.5° to 38° ; dog, cat, 38.5° to 39° ; sheep, rabbit, 38° to 39.5° ; mouse, 37.5° ; rat, 37.9° . Birds have a higher temperature, about 42° C. The temperature varies a little in different parts of the body, that of the interior being greater than that of the surface; the blood coming from the liver, where chemical changes are very active, is warmer than that of the general circulation; the blood becomes rather cooler in its passage through the lungs and the skin.

The temperature also shows slight diurnal variations, reaching a maximum about 4 or 5 P.M. (37.5° C.) and a minimum about 3 A.M. (36.8° C.), that is, at a time when the functions of the body are least active. If, however, the habits of a man are altered, and he sleeps in the day, working during the night, the times of the maximum and minimum temperatures are also inverted. Inanition and inactivity cause the temperature to fall, and just at the onset of death it may be below 30° C. Active muscular exercise raises the temperature temporarily by about 0.5° to 1° C.

Since the temperature of the body depends on the difference between the amount of heat produced and the amount lost, we shall

now consider heat production and heat loss in turn, and then study the way in which these are normally adjusted for the maintenance of a nearly constant temperature in the homoiothermal animal.

Heat Production.

(1) *Effect of Changes of External Temperature.*—In theory there is a fundamental difference between cold- and warm-blooded animals in their reactions to external temperature. A cold environment, since it lowers the temperature of the poikilothermic creature, reduces the metabolism of all its tissues, and thus reduces its heat production.

The warm-blooded individual reacts in precisely the opposite way. Since his temperature remains constant, his heat production increases, in order to neutralise the effect of his cold surroundings. This has been demonstrated in the case of fasting dogs. An example may be given:—

Temperature of air.	13·8° C.	14·7° C.	17·3° C.	18° C.
Heat production in calories per kilo per diem . . .	78·7	74·7	69·8	67·1

In practice it is doubtful whether any such exact relation can be discerned in man, as it may be masked by other factors. We have already insisted upon the equality between the respective energy-values of the food eaten and of the heat produced, and upon the advantage of an ample diet. In practice it is the amount of food taken which controls the heat production, rather than the reverse. The majority of well-to-do people, whose appetite is stimulated by their palate, maintain a constant body temperature by regulating the loss rather than the production of heat. In this connection the following figures, derived from observations made upon a dog which was fed upon considerable quantities of meat, may be compared with those obtained when the same animal was fasting.

Temperature of air.	7° C.	15° C.	20° C.	25° C.	30° C.
Calories per kilo per diem—dog } fasting }	86·4	63·0	55·5	54·2	56·2
Calories per kilo per diem—dog } given 320 g. meat = 81 calories per kilo }	87·9	86·6	86·2	...	83·0

In the fasting dog a lowering of the surrounding temperature increases heat production in the animal; in the well-fed dog this is hardly noticeable.

On the other hand, it is instructive to note the types of food eaten by the natives of different climates. The Hindoo, who eats rice, requires to produce much less heat than the Eskimo, who makes seal meat and blubber his staple articles of diet.

The Seat of Heat Production.—While we say that every living tissue produces heat according to its activity, certain organs, such as glands, produce an amount which is fairly constant although relatively small. By far the largest and most variable amounts are produced by the muscles, and under conditions of extreme cold, increased muscular tone (contraction) and shivering assist in the maintenance of body temperature. On hot days we experience a certain general flabbiness and lack of desire to do muscular work.

Heat Loss.

Heat is lost in several ways—by the respiratory tract, the skin, and the excretions, but the first two are those capable of greatest variation.

Respiration.—In animals which do not sweat much this channel is of special importance, as is well seen in the dog and the sheep, in which there is a rapid respiration when overheated. If the need for heat loss has not been accompanied by exercise, the respiration may be very shallow and this appears to be associated with an exaggeration of the Hering-Breuer reflex. At the same time there is an increased secretion of saliva which keeps the mouth and tongue moist. The tongue is commonly put out.

The skin may regulate its heat loss by changing the amount of blood passing through it. We are familiar with the flushing of the skin after exercise, due to vasodilatation. In such circumstances the body loses a greater amount of heat by radiation, conduction, and convection.

Many years ago it was shown that if an animal is varnished it will die from excessive loss of heat, partly as a result of vasodilatation of the skin vessels, but chiefly because of the loss of the fur which retains heat. It will survive if wrapped in cotton-wool.

If the body is exposed to cold there is good evidence that *adrenaline* may be secreted, for it can be shown that the denervated heart is accelerated and skin vessels are constricted. This does not occur if the adrenals are removed. There is, however, after such removal, a much greater increase in the heat production by shivering (Cannon, Britton and others). In man this seems to be of less importance than in the cat, for the cardiac acceleration is negligible

except during shivering (Barcroft and Verzár). Metabolism is also stimulated.

Sweating.—When the body temperature tends to rise the sweat-glands secrete and the evaporation of the sweat, the latent heat of which is obtained from the body, causes cooling. Wet clothes have a similar effect to sweating, but have the disadvantage that they may occur in the absence of physical exercise and so reduce body temperature that there is great liability to infection by any bacteria which happen to be present in the body. It has been calculated that as much heat may be lost from wet feet as is produced by the body at rest. The respiratory tract is particularly liable to be affected because bacteria commonly lurk there and the cold produces vasoconstriction which renders the mucous membrane more easily attacked. The amount of evaporation depends on the humidity of the atmosphere. We are familiar with the increased sweating which occurs on a hot moist day. The hot day, however, has the advantage over the cold day in that the relative humidity of the air is decreased.

The atmosphere may vary appreciably in its cooling power, according to the rapidity with which the air in the immediate vicinity of the body is changed. A draught causes excessive cooling of the body, therefore, by increasing the loss by convection. (This has already been discussed on p. 75, which should be re-read.)

In climates such as West Africa, Persian Gulf, and Malay, where the tropical sun is combined with the moisture-laden wind, the reverse maintains. There the possibilities of heat loss both by radiation and by evaporation are small, and the inhabitant perforce reduces his heat production to a minimum. He lives indoors, and takes as little exercise as possible.

If, however, exercise is persisted in, sweating continues until the blood becomes so concentrated that sweating ceases, body temperature rises rapidly and death from *heat stroke* may occur. Immediate treatment by cooling the body and diluting the blood is essential.

Certain Factors which govern the Relation between Heat Production and Heat Loss.

(1) *Size.*—The quantity of heat produced by mammals of the same size is practically constant. It is not, however, directly proportional to the weight of the animal, nor to the relative size of the individual cells. The size of the cells in a mouse is not very different from that of the cells in a horse, yet a mouse produces 452 large calories per kilogram of body-weight in twenty-four hours, and the horse only 14.5 calories. The mouse thus requires thirty times more food per

unit of body-weight than the horse. The constant factor is heat production per unit body-surface; all well-nourished animals, including man, produce the same number of calories per square metre of surface (Rubner). The body-surface is relatively large in a small animal. The loss of heat is diminished both by the occurrence of fur and by the absence of sweat in the skins of most small animals, and in man the natural conditions may be much modified by artificial ones, such as clothing.

(2) *Age*.—Inasmuch as the young are small, active, and growing, their heat production is relatively large; and further, since the extreme constancy of temperature which an adult man has attained is an evolved characteristic, very young children are subject to changes of body-temperature which would be of much graver import in older people.

(3) *Constitution*.—Individuals differ greatly in their power of heat loss. Apart from differences in size and in the facility of perspiration, there remain such variations as those of compactness of shape, and especially in the amount of adipose tissue with which the viscera are protected.

Regulation of Body Temperature.

The body temperature appears to be regulated by an area in the brain known as the heat-regulating centre. This centre influences the vasomotor and sweating-centres, thereby regulating heat loss from the cutaneous blood-vessels, and possibly the lower centres controlling heat production, *e.g.* those which innervate voluntary muscle. Evidence of this was put forward by Barbour, who showed that if the brain was perfused through the carotid artery with fluids of different temperatures, the corresponding body reactions were obtained and body temperature varied by the vascular reaction produced in the skin. Evidently the thermotaxic centre is extremely sensitive to changes of temperature in the blood flowing through it.

Later it has been shown that if the section of the brain is made below the thalami, temperature regulation is lost, the animal becoming poikilothermal (Magnus). The exact region of the centre is probably the hypothalamus. Similar results are produced by anæsthesia; hence the necessity for keeping an anæsthetised patient warm, but as such an individual cannot feel pain care must be taken not to burn him.

At the same time it must be understood that the centre is also responsive to stimulation of the skin. Exposure of the body to cold, *e.g.* baths at below body temperature, causes shivering before body temperature has fallen. This appears to be due simply to a fall

in the temperature of the nerve-endings of the skin (Liljestrand and Magnus). Local exposure of the body to heat will also cause local sweating. Presumably reflexes are concerned (O'Connor) and provide a more rapid control than would be possible through the blood. This is well seen in rapid diminution of the volume and of the skin temperature of one hand if the other is placed in cold water (Brown-Séquard).

Fever.—Fever is primarily due to a diminished heat loss. An increased heat production occurs in fever, but that this alone does not produce the condition is seen by the fact that in exercise or exophthalmic goitre, in which metabolism is enormously increased, there is only a very small rise in temperature; it is evident that the normal body can get rid of enormous amounts of heat: but in fever the heat-regulating centre is not completely out of order, for it can be demonstrated that a febrile patient shows reactions to heat and cold.

THE HEAT BALANCE.

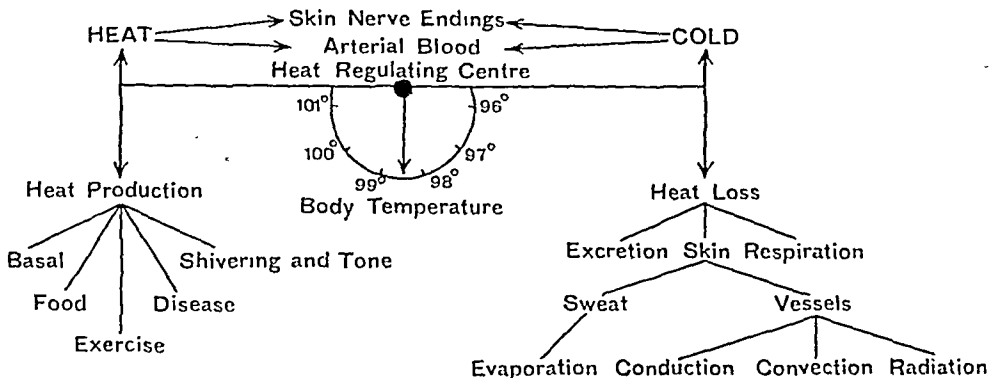


FIG. 183.

It may be that the diminished heat loss is initially due to withdrawal of blood from the skin, *i.e.* when the sickening individual looks pale. Lauder Brunton showed that bleeding would cause a temporary rise of internal temperature in this way. There is, however, at the same time a marked increase of heat production (and of metabolism generally which leads to wasting). The increase may be due to the disease-producing agent itself, but is contributed to by the effect of the rise in temperature on metabolism. Eventually in fever there may be a flushing of the skin, but this is less than normal for the same rise of temperature produced by heating the body.

The withdrawal of blood from the skin may be a result of diminution in the volume of the blood due to the taking up of

fluid by the tissues, a suggestion supported by the fact that the blood becomes more concentrated (Barbour); or it may be that the blood is required elsewhere internally to deal with the infection, the skin vasoconstriction simply compensating for vasodilatation elsewhere.

This explanation of fever indicates why it is that although the heat-regulating mechanism reacts to changes in temperature it appears to be set at a higher level. The withdrawal of blood from the skin necessarily reduces the response to a given degree of higher temperature.

Fever is, however, in a degree protective as antibodies are more actively produced at a higher than at a lower body temperature. The increased metabolism also assists the body to deal more adequately with the infective agents.

Hypothermia.—The body temperature may be lowered in man under narcosis from 5° to 10° C., and maintained at this low level apparently without harm. The state has been found to increase the sense of well-being later.

The sensation of temperature bears no relation to the actual body temperature and depends entirely on that of the nerve-endings of the skin which are affected by the outside air and by the amount of blood in the skin. The pale, shivering patient suffering from a malarial attack may have a temperature of 104° . Similarly, people about to develop influenza look a little pale, and feel a little shivery for the same reason. On the other hand, drugs which cause dilatation of the skin-vessels, *e.g.* alcohol, cause a fall of body temperature, although they give a sensation of cutaneous warmth. After a prolonged hot bath, an individual may feel quite warm, because the skin-vessels become paralysed and may lose so much heat that he "catches a chill" as a result of the lowering of local resistance in the respiratory tract. Experiments on hypothermia under narcosis suggest that local chilling or vaso-constriction is more important than a fall of body temperature as a whole.

Shivering, as we have seen, occurs when the body is cold. It is partly dependent on reflex paths but may occur in a piece of muscle completely removed from the body if a piece of ice is applied to it.

REFERENCES.—Barbour, 1921; Bazett, 1927; Cramer, 1928; and Deighton, 1933.

CHAPTER XLIII

THE CENTRAL NERVOUS SYSTEM

THE central nervous system is contained within the cranio-spinal cavity, and consists of brain and spinal cord. These two parts are continuous with each other, and the line of separation is arbitrarily drawn at the foramen magnum, by which orifice the spinal cord leaves the skull. Both brain and cord are enveloped by three

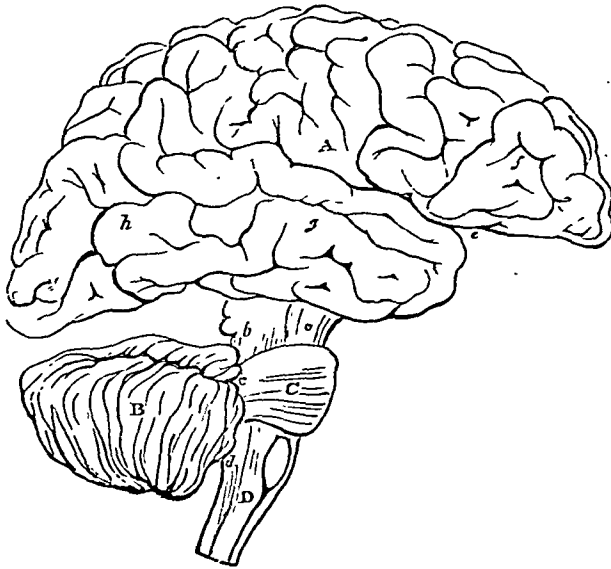


FIG. 184.—Plan in outline of the brain, as seen from the right side. 1. The parts are represented as separated from each other somewhat more than naturally, so as to show their connections. A, cerebrum; *f*, *g*, *h*, its anterior, middle, and posterior lobes; *e*, fissure of Sylvius; B, cerebellum; C, pons; D, medulla oblongata; *a*, peduncles of the cerebrum; *b*, *c*, *d*, superior, middle, and inferior peduncles of the cerebellum. (From Quain.)

connective-tissue membranes, known from without inwards as dura mater, arachnoid, and pia mater respectively.

Anatomy of the Brain.

At the lowest part of the brain (fig. 184), continuing the spinal cord upwards, is the **medulla oblongata** or *bulb* (D). Next comes the **pons Varolii** (C), very appropriately called the bridge, because it appears to join the two halves of the cerebellum or small brain, but in it also are the connections between the bulb and the upper regions

of the brain, and between the *cerebellum* (B), and the rest of the nervous system.

The **mid-brain** comes next (a, b) the ventral part forming the

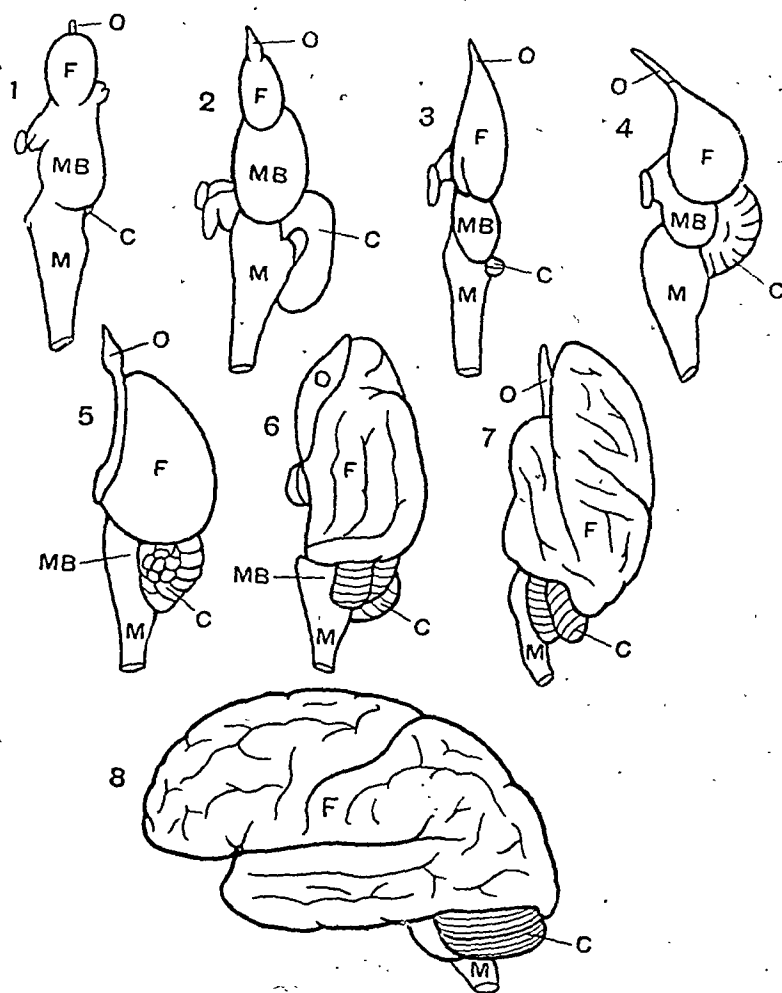


FIG. 185.—The brains of different vertebrate animals. O, olfactory lobe (smell); F, the cerebrum (higher psychical activities); MB, midbrain, and C, cerebellum (co-ordination); M, medulla (control respiration, circulation, etc.).

1. Dogfish.

3. Frog.

5. Rabbit.

7. Monkey.

2. Salmon.

4. Pigeon.

6. Dog.

8. Man.

The size of the brains are obviously not in proportion to each other. Their relative sizes may be judged roughly from the size of their heads which are familiar.

peduncles or crura of the **cerebrum** (A), the largest portion of the brain.

A further figure showing the internal structure of the brain is given in relation to the Cerebro-Spinal Fluid.

But such a complex brain as the human organ does not obtain throughout the vertebrate series. Some idea of this is given in

fig. 185, p. 575, which indicates the changes which are found. In the lowest animals the cerebrum and cerebellum are negligible, but with the development of locomotion and the co-ordination of movement, the cerebellum and mid-brain become more important. They are particularly well seen in fishes and birds which move in three planes. Gradually the importance of the cerebrum increases, becoming at first simple and later more convoluted, until in man it is by far the largest part. It will be seen, however, that throughout the same general plan is retained. It was, however, pointed out by Turner that some mammals have brains of a very primitive type and he emphasised that the internal structure of the brain was more important than the external appearance.

A comparative study of the brain in different animals has been most valuable in the elucidation of the functions of its various parts.

There is some relation between the degree of development of the different parts of the brain and the habits of an animal. For instance, animals which rely largely on the sense of smell for their prey have a large olfactory area; whereas in such animals as the porpoise, which have no sense of smell, the olfactory area of the brain is absent. Animals with keen vision have a large visual area in their brains; animals of nocturnal habits, or which live underground in the dark, have a very small one.

It should, however, be added that so far as the cerebrum is concerned its development confers potential, for those born with the most highly evolved brains do not necessarily use them, and many whose heads do not suggest high development have remarkable powers of mental activity.

CHAPTER XLIV

THE SPINAL CORD AND SPINAL NERVE-ROOTS

THE spinal cord is a column of nerve-substance connected above with the medulla oblongata of the brain, and situated in the vertebral canal. If it is cut across it is seen to be composed of grey matter

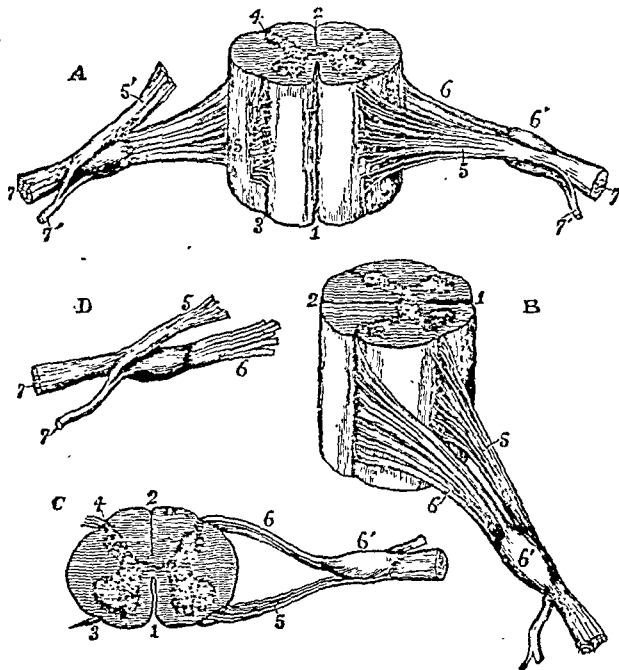


FIG. 186.—Different views of a portion of the spinal cord from the cervical region, with the roots of the nerves (slightly enlarged). In A, the anterior surface of the specimen is shown; the anterior nerve-root of its right side is divided; in B, a view of the right side is given; in C, the upper surface is shown; in D, the nerve-roots and ganglion are shown from below. 1, the anterior median fissure; 2, posterior median fissure; 3, anterior lateral depression, from which the anterior nerve-roots are seen to issue; 4, posterior lateral groove, into which the posterior roots are seen to sink; 5, anterior roots passing the ganglion; 5', in A, the anterior root divided; 6, the posterior roots, the fibres of which pass into the ganglion 6'; 7, the united or compound nerve; 7', the posterior primary branch, seen in A and D to be derived in part from the anterior and in part from the posterior root. (Allen Thomson.)

which on histological examination is found to be composed largely of nerve-cells, and of white matter which is composed of nerve-fibres. The **white matter** is situated externally, and constitutes its chief portion; the **grey matter** is in the interior, and is so arranged that

in a transverse section of the cord it appears like two crescentic masses connected together by the posterior commissure (fig. 186). The apices of each crescent are called the anterior and posterior horns respectively. Throughout the whole length of the cord runs the **central canal**, which opens above into the space at the back of the medulla oblongata and pons, called the fourth ventricle.

The spinal cord consists of two symmetrical halves, separated anteriorly by a median *fissure* and posteriorly by a median septum of neuroglia. It is divided into three portions or columns, an *anterior*, *lateral*, and *posterior*, by columnar extensions of the grey matter. Between the anterior and lateral columns spring the **anterior roots** of the spinal nerves (fig. 186 B and C, 5); and just in front of the groove between the lateral and posterior columns the **posterior roots** enter (B, 6): a pair of roots on each side corresponds to each vertebra or segment. The posterior root is characterised by the ganglion on it. These two roots after a short distance join together to form what is known as a **mixed nerve**. The functions of the roots are dealt with later, but it may be noted here that the anterior is efferent or motor and the posterior is afferent or sensory.

Methods of investigating the Tracts of the Central Nervous System and the Spinal Roots.

(a) It has been possible to trace some tracts *by stimulating* them at one point and observing the effect, and this may be amplified by section of the pathway at various points.

(b) It has been found possible also to follow certain tracts by tracing the course of *action potentials*. Most of our information has, however, been collected by older or more laborious methods.

(c) The *embryological method*.—It has been found by examining the spinal cord at different stages of its development that certain groups of the nerve-fibres put on their myelin sheaths at earlier periods than others, and so the different groups of fibres can be easily distinguished.

(d) *Wallerian or degeneration method*.—This method depends upon the fact that if a nerve-fibre is separated from its nerve-cell it degenerates. It consists in tracing the course of tracts of degenerated fibres, which result from an injury to any part of the central nervous system. When fibres degenerate peripheral to lesion, the tract is one of *descending degeneration*, and when the fibres degenerate in the opposite direction, the tract is one of *ascending degeneration*. By the modern methods employed in staining the central nervous system, it has proved comparatively easy to distinguish

degenerated parts in sections of the cord and of other portions of the central nervous system. Degenerated fibres have a different staining reaction from normal tissue when the sections are stained by the Weigert-Pal method; this consists in overstaining them in a special solution of hæmatoxylin, and then decolorising with potassium permanganate and sulphuric acid. The degenerated fibres appear light yellow, whereas the healthy fibres remain a deep blue. Marchi's osmic acid method has already been referred to on p. 56. Accidents to the central nervous system in man have given us much information on this subject, but this has been supplemented and largely extended by experiments on animals, particularly on monkeys, and considerable light has been shed on the conduction

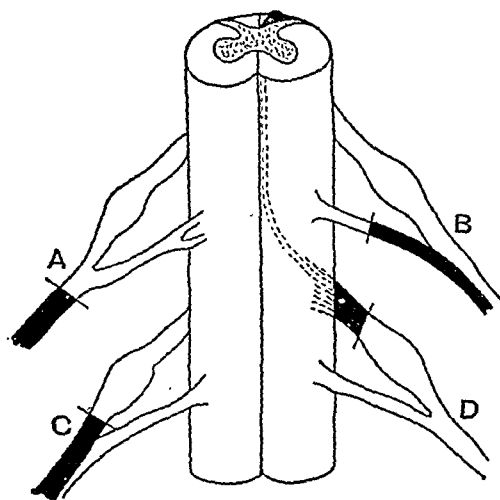


FIG. 187.—Diagram to illustrate Wallerian degeneration of nerve-roots.

of impulses to and from the nervous system by the study of the results of section of different parts of the central nervous system, and of the spinal nerve-roots.

By the degeneration method it has been possible to show that the anterior root is composed of the axons of cells in the anterior horn of the spinal cord and that the posterior root is composed of axons of cells which are situated in the ganglion of the posterior roots. Separation of the axons from their parent cells results in degeneration of the distal end of the axons. These facts, made out by the elder Waller, are illustrated by fig. 187 in which:

A represents a section of the mixed nerve beyond the union of the roots; the whole nerve beyond the section degenerates, and is consequently shaded black in the figure.

B represents the result of section of the anterior root; only the anterior root-fibres degenerate; the sensory fibres of the posterior root remain intact. The small medullated nerve-fibres

(not shown in the diagram) also degenerate as far as the ganglion cells of the sympathetic system with which they communicate.



FIG. 188.—Groups of fibres from the anterior and posterior roots several days after section of both roots close to the cord; the anterior fibres are degenerated; the posterior, being still in connection with the nerve-cells from which they grew, are normal.
(Mrs Waller for Dr Waller.)

Some recurrent sensory fibres in this root do not degenerate with the others, but are found degenerated in the part of the anterior root attached to the spinal cord.

Section of the posterior root always produces the same physiological effect (loss of sensation) wherever the section is made, but the degeneration effect is different depending on whether the section is made on the proximal or distal side of the ganglion. If the section is made beyond the ganglion, the degeneration occurs as shown in C beyond the section in the peripheral portion of the posterior root-fibres; the anterior root remains intact except for the recurrent sensory fibres which it contains.

If the section is made as in D (fig. 187), the posterior roots degenerate between the ganglion and the cord, and if several posterior roots are so cut the degeneration may be traced into the cord. In this case a part of the cord known as the column of Burdach can be degenerated as far up

as the medulla oblongata. In this way the exact situation of a number of tracts or bundles of nerve-fibres has been shown. They are indicated in figures. The detailed position of these tracts is now more properly dealt with in Anatomy.

CHAPTER XLV

THE REFLEX ACTIVITIES OF THE ANIMAL

THE function of a nervous system, however simple or however complicated, is to adjust the activities of the animal within itself and towards its environment. It is the function of the central nervous system to receive impulses by means of the afferent nerves, to correlate them, and to send out appropriate stimuli by the efferent nerves to the various parts of the body.

A large amount of this adjustment takes place without conscious effort and is purely automatic or reflex. We may indeed look upon the reflex as being the physiological unit of the nervous system. A **reflex** may be defined as the response by an effector organ to a stimulus received by a receptor and transmitted by a conductor which is itself incapable of the end-effect. It depends, as we have seen, on a chain of neurones.

In considering the nervous system of an animal from this point of view, we are reminded of that of a simple segmented animal, such as a crustacean, where it is evident that, while each segment has a considerable degree of local control, by means of connecting fibres the various segments may act in unison for the benefit of the animal. A very similar, but more elaborate mechanism is seen in the higher animals, and it will be seen that each part of the nervous system exercises a certain degree of local control, yet is connected and acts when necessary with the higher parts of the system.

Before studying reflex action in detail it is convenient to consider briefly the functions of the spinal cord and its roots. As would be expected from what has been said above, the spinal cord connects together different parts of the nervous system and at the same time is a centre for local control or reflex action.

The Functions of the Spinal Cord.

These functions will be considered in more detail later and need only be summarised at this stage.

As an **organ of conduction** the spinal cord carries impulses to and from the brain, some of which are related to conscious activity

and others to more automatic or reflex activities of the body, such as the maintenance of posture. The actual pathways concerned have already been described.

In addition, the **association tracts** link together various levels of the cord and bring about co-ordination of activity between different levels of the body.

As a **reflex centre** the cord brings about a considerable correlation of the activities of the animal. For the most part these are concerned with the protection of the animal, with movements, such as walking, and with the control of the excretory mechanisms of the bladder and rectum. The actual reflexes are dealt with in detail below.

Functions of the Roots of the Spinal Nerves.

Each spinal nerve, we have seen, originates from the spinal cord by two roots. The *anterior* or *ventral* root consists of nerve-

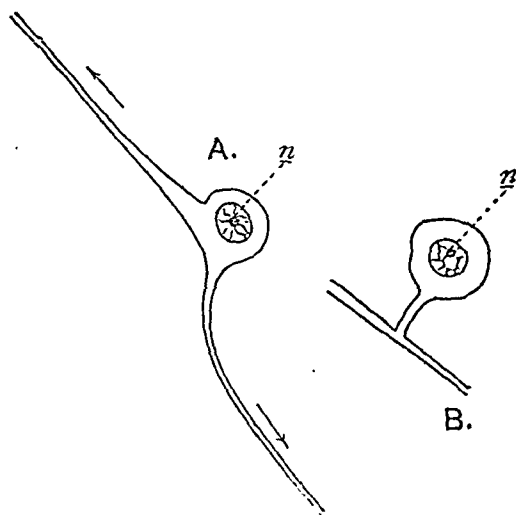


FIG. 189.—A, Bipolar cell from spinal ganglion of a 4 weeks' embryo; *n*, nucleus; the arrows indicate the direction in which the nerve processes grow, one to the spinal cord, the other to the periphery. B, a cell from the spinal ganglion of the adult; the two processes have coalesced to form a T-shaped junction. (Diagrammatic.)

fibres which originate from the large multipolar cells in that portion of the grey matter in the interior of the spinal cord which we call the anterior horn. These nerve-fibres are all medullated; the large ones join up with the posterior root to form the spinal nerve; the small nerve-fibres leave the root and pass to the sympathetic chain, which then distributes non-medullated fibres to the involuntary muscles of the blood-vessels and viscera.

The other root, the *posterior* or *dorsal* root, has upon it a collection of nerve-cells forming the spinal ganglion.

From the cells in the ganglion two processes take origin. In the embryo these are separate but in the adult form they are fused, forming a T-shaped junction (fig. 189, B).

The discovery that the anterior roots are motor and the posterior sensory is usually attributed to Bell (1811); but an examination of his writings shows that the deductions he drew were incorrect;

it was Magendie (1822) who gave the first unassailable description. Similar observations in regard to the cerebral nerves were first made by Mayo.* Magendie found that on section of the anterior roots there was paralysis of the muscles supplied by the nerves; on section of the posterior roots there was loss of sensation. These experiments clearly pointed to the conclusion that the anterior roots contain the efferent (motor) fibres; and the posterior roots the afferent (sensory) fibres. This conclusion was confirmed by the experiment of stimulation. Stimulation of the peripheral end of the cut anterior root caused muscular movement; of the central end, no effect. Stimulation of the central end of the cut posterior root caused pain and reflex movements; of the peripheral end, no effect on voluntary muscle.

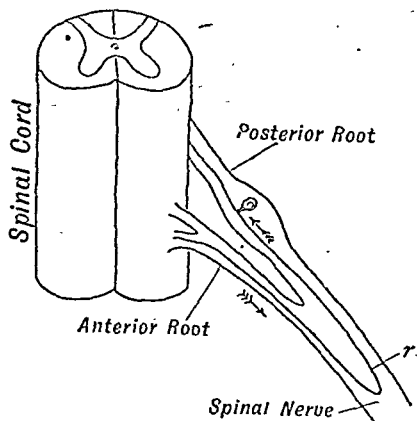


FIG. 190.—Diagram to illustrate recurrent sensibility. See text.

The latter causes vascular dilatation (see Autonomic Nervous System).

Recurrent sensibility.—One of the statements just made requires a slight modification, namely, that excitation of the peripheral end of a divided anterior root will evoke pain and what are known as reflex movements, as well as direct movements; that is to say, the anterior root, though composed mainly of motor fibres, contains a few sensory fibres coming from the membranes of the spinal cord, and then running into the posterior root with the rest of the sensory fibres. They often, however, run down the mixed nerve a considerable distance before returning to the posterior roots.

The preceding diagram (fig. 190) illustrates the course of one of these recurrent fibres (*r*); the arrows represent the direction in which it conveys impulses.

REFLEXES.

It has already been stated that the reflex may be considered the physiological unit of the nervous system. It has been usual to classify reflexes anatomically according to the amounts of the nervous system which they involve, but it is really best, however, to classify them physiologically, which is also their order of phylogenetic appearance.

1. **Protective Reflexes.**—These are seen in all animals and protect the animal from injury by withdrawing the stimulated part. Most involve the spinal cord but some the brain stem. They are brought into operation by harmful stimuli.

2. **Antigravity Reflexes** maintain the rigidity of the limbs against the force of gravity. They involve the spinal cord and the medulla.

3. **Righting Reflexes** adjust first the position of the head to

* Mayo was the first Professor of Physiology in King's College, London.

the earth's surface, then the position of the trunk to the head, and the position of the limbs to the body. These reflexes involve the spinal cord, medulla and mid-brain. Like the antigravity reflexes they are brought about by proprioceptive stimulation from the body itself, especially from the muscles and tendons.

4. **Conditioned Reflexes** result from experience. The significance of the sensory stimulus depends on the circumstances in which the stimulus was previously experienced. Here the cerebrum, as well as the lower parts of the nervous system, are concerned.

The discovery of reflex action was made by Marshall Hall (1833), a physician in London, who during his lifetime never received adequate recognition of his work. The antigravity reflexes were first described by Sherrington, in 1898. He was originally a bacteriologist but subsequently became Professor of Physiology at Liverpool and later at Oxford. He and his pupils made a study of spinal reflexes generally. The righting reflexes were elucidated chiefly by Magnus, Professor of Pharmacology in Utrecht, while the importance of the conditioned reflexes was first appreciated by Pavlov in Moscow. (See references.)

The Protective Reflexes.

The simplest form of reflex activity known is the **axon reflex**, which does not involve the central nervous system and is concerned with the protection of the skin. If an irritant, *e.g.* a mustard plaster or croton oil, is applied to the skin, a reddening due to dilatation of blood-vessels is produced. If the nerve-supply is cut, as is sometimes done by surgeons to relieve pain, *e.g.* in neuralgia of the 5th nerve, the reddening on application of the irritant can be obtained for a few days but is no longer possible after the peripheral fibres have degenerated. This demonstrates the dependence of the action on a local nervous mechanism, apparently in the peripheral part of the axon: the axon appears to divide, giving a branch to the skin and another to the wall of a blood-vessel. It may be, however, that the sensory impulse somehow passes to vasodilator fibres which we know are distributed from the sensory posterior nerve-roots.

The **spinal protective reflex** is the simplest form of reflex involving the central nervous system. It depends on the co-operation of a receptor organ, an afferent sensory nerve, a chain of nerve-cells in the spinal cord, an efferent motor nerve, and an effector organ, the whole constituting the reflex arc (see figs. 31 and 198).

Although a spinal reflex is usually described it must be understood that reflexes of this type are obtained from cranial nerves—notably the corneal reflex by which the eye is protected.

The reflex activities of the spinal cord may be studied in a **spinal animal**, i.e. an animal in which the brain has been destroyed or the spinal cord cut across in the cervical region. In the case of a mammal artificial respiration is necessary since the respiratory centre is cut off, unless the section is made below the origin of the phrenic nerves.

The simplest way to produce a typical spinal mammal is to clamp the vertebral and the carotid arteries and allow time for the anaesthesia to pass off. (See fig. on p. 600.)

A cat so operated upon, after a short period of shock has passed off, assumes a characteristic position of flexion; it curls up (fig. 197).

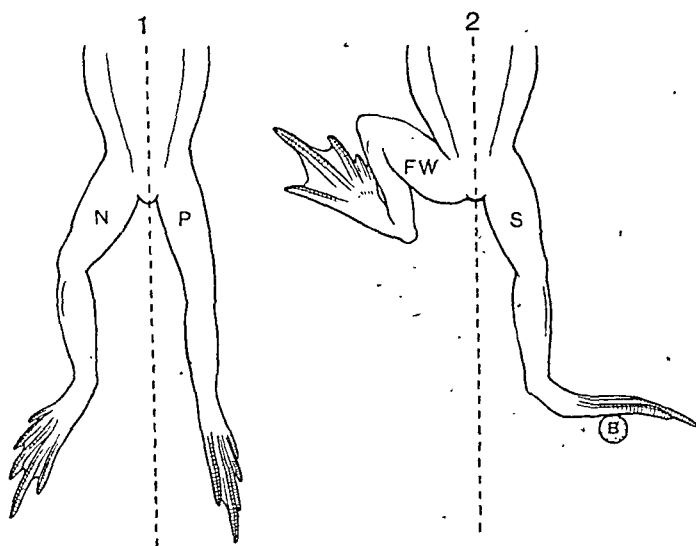


FIG. 191.—Reflexes in the frog (diagrammatic). In 1 the normal reflex tone N of the legs as indicated by the partial flexion at the knee is seen. This is absent if the spinal cord is destroyed, P. In 2 is seen the flexion withdrawal reflex. FW is the response to a harmful stimulus and the thrust reflex S to a blunt object, B.

If a limb is pinched or pricked it is at once withdrawn (**flexion withdrawal reflex**). This is obviously a defence reflex to remove the limb from the injuring force or noxious stimulus. Sometimes the stimulus throws the whole animal into extreme flexion (mass reflex).

After a period of absence of reflexes after operation a spinal animal may also show extensor reflexes also (fig. 191).

After destruction of the brain of a frog the shock of the operation renders the animal for a variable time motionless and irresponsive to stimuli, but later on it gradually assumes a position which differs but little from that of a conscious animal. If thrown into water it will swim; if placed on a slanting board it will crawl up (Goltz); if stroked on the flanks it will croak (Goltz); if it is laid on its back, and a small piece of blotting-paper moistened with acid is placed on the skin, it will generally succeed in kicking it off; if a

foot is pinched it will draw the foot away; if left perfectly quiet it remains motionless. (Sherrington, 1920; Creed, Denny-Brown, Eccles, Liddell, and Sherrington, 1932.)

The Protective Reflexes of Man.

The occurrence of many protective reflexes in man similar to those in animals are facts of everyday experience. The flexion withdrawal reflex may be elicited during ordinary sleep or light anæsthesia. It is also obtained in individuals suffering from paralysis due to injury to the pyramidal tracts and who may be *unable to move the part voluntarily*.

The Extensor Antigravity Reflexes.

These reflexes are most conveniently seen in an animal whose brain stem has been cut across just above the pons (see Decerebrate Animal), but they are also obtained from a chronic spinal animal, that is, an animal whose spinal cord has been cut across some time previously and in which the shock of the section has passed off. Normally the activity of the reflexes is reduced by the activity of the cerebrum, hence the necessity for its removal.

The pathways on which they depend are similar to that of the simple spinal arc, but in addition there are pathways to (spino-vestibular) and from (vestibulo-spinal) Deiters's nucleus, *i.e.* the lateral vestibular nucleus in the upper part of the medulla.

The Stretch Reflexes.—These are the reflexes which keep the legs of the animal straight in standing and are normally found, as would be expected, in the extensor muscles. They may be demonstrated by stretching a muscle, as by sudden bending of the leg, or by tapping a tendon. As these facts suggest, they are set up by impulses from the muscles themselves, and this is proved by the fact that they are abolished by section of the posterior roots through which the impulses from the muscles pass. Moreover, if a muscle is denervated and attached to a lever by which its tension may be measured it is found that when stretched it develops much less tension (not more than 20 per cent. due to its elasticity) than when its nerves are intact. The reflex is not abolished by local anæsthesia of the tendon. Many reflexes of this type occur but the thrust reflex and crossed extensor reflex may be taken as examples. They are also the bases of the postural reflexes which are discussed in a later section.

The thrust reflex is seen if a sudden force is applied to the foot so as to bend the leg. This causes the quadriceps extensor in the front of the thigh to contract and the limb to straighten

The importance of this reflex in propelling the body forward in walking is obvious. (See also S in fig. 191.)

The *crossed extensor reflex* is seen in the quadriceps extensor of the thigh when the corresponding nerve of the opposite side is stimulated. It, too, is part of the walking mechanism since the lifting of one leg requires increased contraction of the muscles of the other to maintain the weight of the body. The crossed extensor reflex is dramatically inhibited by stimulation of a sensory nerve of the same side (fig. 192).

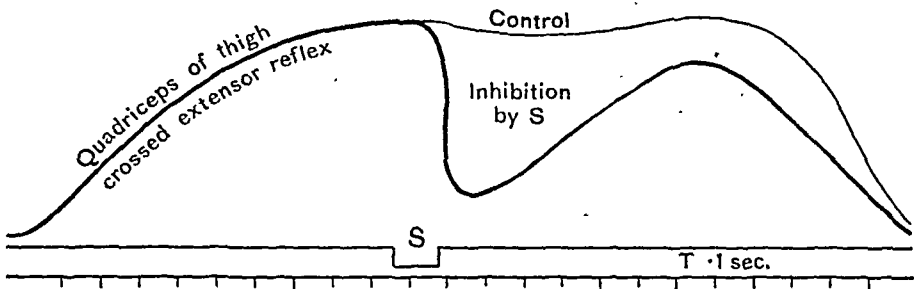


FIG. 192.—Records showing inhibition of the crossed extensor reflex in the cat. (Drawn from two records by Liddell and Sherrington.)

Difference between the Flexor and Extensor Reflexes:—

Flexor reflexes, being protective, are more immediate and rise to a maximum more rapidly than extensor reflexes which rise slowly. In so doing they are said to demonstrate recruitment as they apparently bring into action more neurones and muscle fibres as the stimulus is kept up. This is possibly an adaptation to the load to be borne and appears to be a "self-braking" action in such reflexes, for if the afferents of the executant muscles are cut the contraction is speeded up. Extensor reflexes show a long after-discharge (see p. 590), presumably because of their reaching their maximum slowly.

In the extensor reflexes the slow acting red muscles (see p. 15) play a predominant part, but white fibres may also be used. It is this use of the red muscles which makes the extensor reflexes less liable to fatigue; indeed, a single unit may go on discharging at a slow rate, 5-8 per second indefinitely.

The Sensory Nerve-endings in Muscle.

From what has been said of the extensor reflexes it is evident that there are important sensory nerve-endings in muscle and allied tissues. These were found histologically by Ruffini (1898) and by Golgi. They are studied in relation to Sensation in general later.

The Properties and Characteristics of Reflex Arcs.

Reflex arcs have certain characteristics which may be seen in the study of the spinal reflex. These are of importance, as there is reason to believe that similar characteristics are exemplified in higher arcs also. Most of these characteristics, it will be seen, really depend on the properties of the region of the synapse; indeed, much of our knowledge of this region has been obtained from the study of reflexes. The synapse is discussed in a separate section below.

Resistance.—If the time which a reflex ought to take be calculated from our knowledge of the rate of the nerve impulse as conducted by nerve-fibres, it is found that the actual time taken is appreciably longer. This extra time or *reduced reflex time* has presumably been spent in traversing the central nervous system and especially in passing across the synapses or junctions between one neurone and another. It has been calculated that the time lost at a synapse is 0.002 sec.

Effect of Repetition of Stimulus.—Once a reflex has been evoked it is found that it becomes, up to a point, increasingly easy to elicit it, and the reduced reflex time becomes lessened. This is known as **facilitation**. This fact is of obvious importance in relation to increase of skill in various manual occupations. Beyond this point, however, **fatigue** may readily set in. This must occur on the central part of the arc, at the synapse, since nerve is not fatiguable in the ordinary sense; it is found that when fatigue is present and a reflex can no longer be elicited, the muscle concerned can still be made to contract through its nerve or through another afferent nerve. Fatigue of a spinal reflex appears to be recovered from with remarkable speed, provided the blood circulation is good.

Summation.—Although a stimulus may be insufficiently strong to elicit a response, the repetition of the stimulus may be effective. The fact suggests that there is an accumulation of excitatory states (see p. 592) centrally or peripherally at the point of stimulation. Thus it may be possible to bring about a response with two separate subliminal stimuli, each of which is insufficient; or, if each is sufficient, the total effect will be greater than with each independently.

Summation of chemical stimuli is well illustrated by Türck's method. If a number of beakers of water are prepared, acidulated with 1, 2, 4, etc., parts of sulphuric acid per 1000, and the tips of a spinal frog's toes are immersed in the weakest, the frog does not at first respond, but in time the cumulation or summation of the sensory impulses causes the animal to withdraw its feet. If this is

repeated with the stronger liquids in succession, the time that intervenes before the muscles respond becomes less and less. This method also serves to test reflex irritability when the frog is under the influence of various drugs.

Dependence on Oxygen.—We have noted that fatigue may set in if a stimulus is too often repeated. If, however, the oxygen supply is deficient, it sets in more readily. Synapses are apparently particularly sensitive to the effects of oxygen-want. A fall of blood-pressure markedly depresses the reflexes, which disappear in man when the mean arterial pressure drops below 50 mm. Hg. It is possible that the height of the blood-pressure is of considerable importance in relation to nervous activity, but it is extremely difficult to obtain definite data on this point.

Dependence on Carbon Dioxide.—Some reflex arcs, *e.g.* those concerned with posture, require carbon dioxide as is shown by the fact that if the carbon dioxide is washed out by over-ventilation the reflexes disappear. It is probable that in part at least this apparent dependence on carbon dioxide is really that this gas facilitates, as we have seen, the unloading of oxygen from the blood.

Spread.—The effect of a given stimulus which is capable of evoking a reflex depends very largely on its strength. A relatively weak stimulus may cause a simple response confined to one limb, but a stronger stimulus may spread not only to the opposite side but also to the adjacent segments of the cord, bringing about a generalised movement. It appears likely that in the first instance the afferent impulses take the easiest path, which suggests that the resistance of the synapses in the various paths may vary appreciably. It is considered that such a grading of synapses may play an important part in the general activity of the nervous system.

Local Sign.—If a portion of the body be stimulated, *e.g.* the flank pinched, it is observed that the reflex is definitely purposeful and the movement is directed towards the removal of the stimulation. Thus a piece of blotting paper soaked in dilute sulphuric acid and placed on the flank of a decapitated frog, is removed by the reflex activity of its hind foot.

Unidirectional Conduction.—We have noted that a nerve impulse may be carried in both directions along a nerve. In a reflex arc the impulse can go in one direction only.

Inhibition.—One reflex can inhibit another, the reflex more important for the welfare of the animal predominating. This we have already seen in relation to the crossed extension reflex. It is also evident in regard to the scratch reflex (p. 613) in which one protective reflex predominates over another. The inhibition

of a sneeze by firm pressure on the upper lip is a similar phenomenon.

The Nature of the Reflex Response.—If a motor nerve is stimulated by a single shock the resulting response is a muscular twitch. If a tetanising current of short duration is applied to a motor nerve all the muscle-fibres supplied contract at once and the tension rises and falls abruptly. If, however, the same stimulus is used to actuate it reflexly the rise and fall of tension are more gradual as more nerve and muscle units come into action and are released. This is specially well seen in the antigravity reflexes and is very characteristic of reflex action. It should perhaps be added

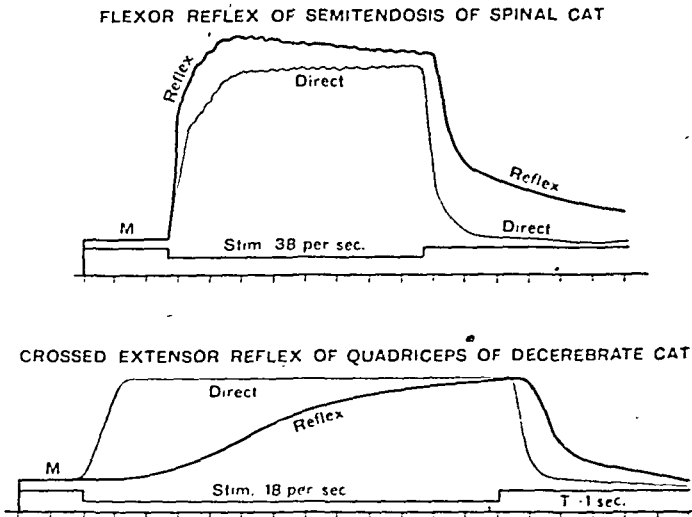


FIG. 193.—Upper—A typical flexor response. Lower—A typical extensor response. (Drawn from four records by Liddell and Sherrington.)

that in order to demonstrate such rapid changes it is necessary to use a photographic recording system as the inertia of an ordinary lever system is too great. The movement or other activity produced reflexly does not cease directly the stimulus is removed, but continues for a time after cessation of stimulation. This phenomenon is called **after-discharge**, and is one of the most striking features of reflex action.

If during tonic contraction an inhibitory afferent nerve is stimulated, the contraction at once becomes less, but the muscle again contracts the moment the inhibitory stimulus is removed, often to a larger extent than before. This is known as **rebound**, but is a very variable phenomenon (see fig. 202).

There is considerable overlapping in reflexes. (See the Motor Unit and Motoneurone Pool.)

It will be realised that many of the characteristics of reflexes depend on the synapses concerned.

The Action of Drugs on Reflexes.

Reflexes are enhanced by strychnine and diminished by bromide, which apparently acts on the resistance of the synapse. It is of interest that these drugs are used commonly in medicine, strychnine to enhance and bromide to depress the activity of the nervous system. Nicotine paralyses the transmission of impulses at the synapses in autonomic ganglia (see p. 79) and is responsible for the harmful effects of the excessive smoking of tobacco.

The Synapse.

It has become increasingly evident that the region of the synapse is of great functional importance. The term was introduced by Foster and Sherrington in 1897 and is derived from a Greek word meaning "a clasp."

The structure of the synapse is not usually dealt with adequately in books on Histology, and is of interest at this stage. Detailed histological study of the synapses was at first disappointing in the mammalian nervous system. It was thought at first that there might be nervous strands between the neurones, and this view was held particularly by Golgi of Milan, but all later methods have failed to show such strands and the evidence from degeneration indicates that structurally each neurone is distinct from the others in its vicinity (Waldeyer, 1891). Increasing attention has, however, been paid to the nerve terminals.

It was originally shown by Ramón y Cajal in Madrid, that at the junction between some neurones the terminations of axons were enlarged to form "boutons" which lie close to adjacent nerve-cells as indicated in fig. 194*a*. The existence of these "pieds terminaux," as they are also called, has now been generally confirmed and accepted, but they are best seen in the lower animals (fig. 194*b*). When cut off from their parent cells the "boutons" swell up to about twice their size and degenerate. (See Fulton, 1938.)

The Properties of the Synapses.—The conception of humoral transmission at synapses (p. 65) makes it possible to assume that the "boutons" have a special function in bringing about the release of the chemical mediator to which the next nerve-cell is peculiarly sensitive, and it would be easy to account for the properties of the synapse in terms of the accumulation and continuance of the action of a chemical transmitter, and to show how it might be responsible for these properties, which are:—

1. Synaptic resistance or reflex latency (see p. 588).
2. Prevention of spread of the self-propagating nervous impulses within the nervous system.
3. Provision of pathways of varying resistance within the nervous system which by repeated use may become "canalised."
4. Summation or the additive effects of repeated stimuli.

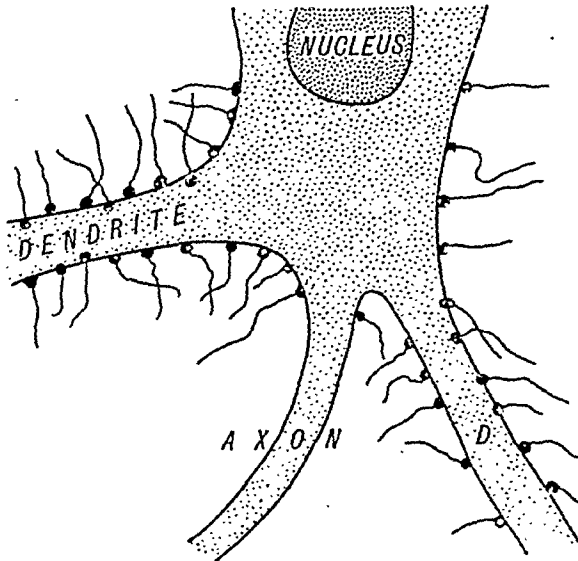


FIG. 194a.—Showing "boutons" on a nerve cell at the end of fibrils from other cells (Raymón y Cajal.)



FIG. 194b.—Diagram of the "boutons" from the nervous system of the gold-fish. (Bodian.)

5. Excitatory state (an accumulation of chemical mediator at the synapses concerned).
6. After-discharge, a continued action of the chemical mediator.
7. Unidirectional conduction in reflex arc and other pathways involving a synapse.
8. Refractory period.

Some recently discovered facts do not, however, entirely support the view that the chemical mediator is acetyl-choline, as first thought, although this substance may be concerned. For example, by study of the transmission through autonomic ganglia where synapsing occurs, it has been stated that when the preganglionic fibre is

stimulated the excitation of the post-ganglion fibre precedes the release of the acetyl-choline (Lorento de No), while Eccles has been unable to find that eserine which affects the action of acetyl-choline elsewhere affects synaptic delay. These workers postulate that something like an electrical charge accumulates at the region of the central cell and is "detonated" by afferent impulses. It may be shown that it is more correct to speak of an accumulation of excitatory ions.

It is important to realise that there are probably many synapses in reflex arcs, not only so but there may also be alternative pathways through internuncial (short connecting) neurones which probably play an important part in determining the priority of impulses in competition for the control of the anterior horn cells of the motoneurones.

The Motor Unit and the Motoneurone Pool.

In the introductory section on the nervous system the illustration of the reflex arc (fig. 31) has, for simplicity, been given in terms of one cell of the anterior root passing out to a muscle. By cutting the posterior root and allowing time for degeneration it has been possible to count the number of nerve-fibres passing to a muscle and to compare it with the number of muscle-fibres. In some instances it has been found, by Eccles and Sherrington, that a simple large nerve-fibre may supply from 140 to 160 muscle-fibres, but smaller nerves might supply smaller units of 5-10. In a muscle there may be several hundreds of such units which are innervated from a group of anterior horn cells which the Oxford School have designated its "moto-neurone pool." The cells of the pool are operated by impulses from the descending tracts from the brain and from a variety of sensory regions in their own segment, from segments above and below and from the opposite side. Two or more afferent fibres may operate the same group of cells of the pool and produce **occlusion**. This accounts for the fact that the tension developed reflexly by the stimulation of two afferent nerves may be less than the sum of each separately. Similarly, since any afferent nerve only operates part of the pool its stimulation can never produce as much tension as is produced by stimulation of the whole motor nerve. This phenomenon of **fractionation** recalls the fact that voluntary effort does not call forth the greatest tension possible. The overlapping of the areas operating in the pool also explains why certain pairs of afferents when excited by subminimal stimuli may produce excitation, but when other neurones are excited the stimulation is ineffective.

The Tendon Reflexes in Man.

The tendon reflexes of man are of special interest and importance because of the easy method by which they can be studied and because their absence or exaggeration is often an indication of the presence of injury or disease of the spinal cord. In this connection it is the purely spinal component of the reflexes which is of most importance, although as we have seen in relation to the extensor reflexes generally, they are really but part of a more elaborate antigravity mechanism with pathways to and from Deiters' nucleus in the medulla. Thus the reflex, although described as a

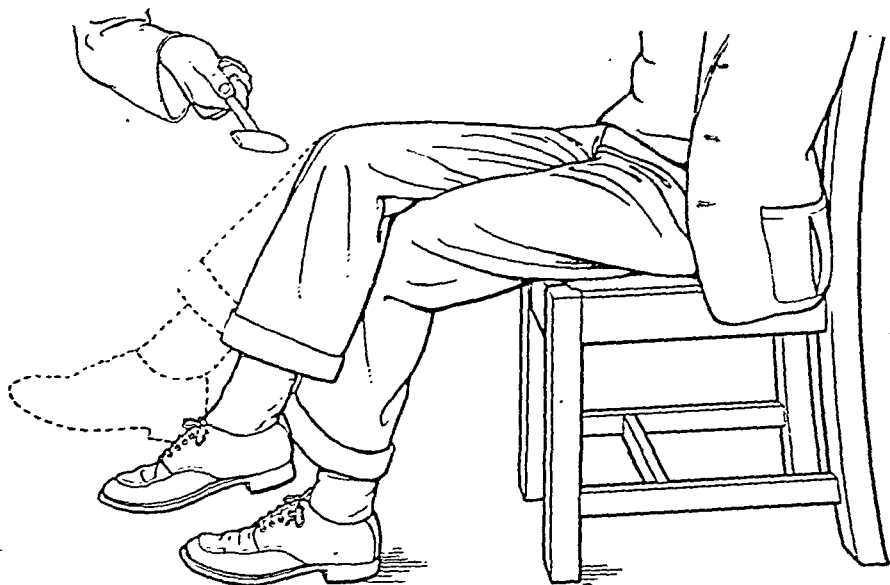


FIG. 195.—The taking of the knee-jerk.

spinal reflex, is really a fractionated antigravity reflex. In each case it is brought about by stimulating the nerve-endings in the tendon mechanically. It will be realised that physiologically this is a very abnormal stimulus.

The knee-jerk.—The quadriceps muscle is slightly stretched by putting one knee over the other; a slight blow on the ligamentum patellæ causes a movement of the foot forwards, as indicated in the dotted line of fig. 195. The reflex is present in health.

The *ankle-jerk* is one of importance, for in such diseases as locomotor ataxy (tabes),* in which the tendon reflexes are lost, it usually disappears before the knee-jerk. It is best elicited if the patient kneels with one knee upon a cushioned chair, whilst

* Tabes dorsalis or locomotor ataxia is a late manifestation of syphilis produced by degeneration of the posterior root ganglia and posterior horns.

standing on the other leg by the side of the chair. The calf muscles of the kneeling leg are thus slightly stretched by the weight of the foot, and a sharp tap upon the tendo Achillis elicits the jerk.

Jerks of the biceps, triceps, and supinator of the upper limb may also be elicited in a similar way, but they are not normally so active. The jaw-jerk, which causes the open lower jaw to close sharply when its point is tapped, is only present when the path to the motor nucleus of the 5th nerve is involved.

Ankle-clonus.—This is elicited as depicted in the next figure: the hand is pressed against the sole of the foot, the calf muscles are thus put on the stretch and they contract, and if the pressure is kept up

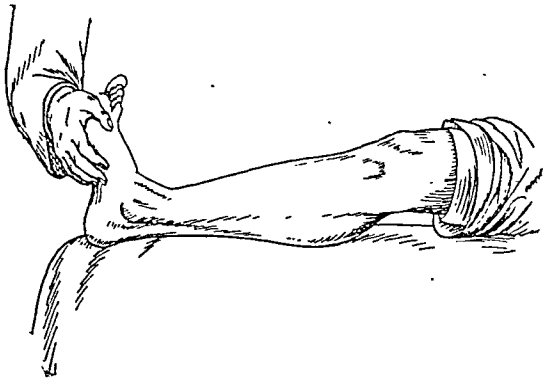


FIG. 196.—Ankle-clonus. (M. Barclay Smith.)

a quick succession or clonic series of contractions is obtained. This is not readily obtained in health.

The exact course of the reflex arc concerned in the **knee-jerk** has been worked out by Sherrington in the monkey. The nerve-fibres are mainly those which pass (1) to and from the extensors* by the anterior femoral nerve, and (2) to and from the hamstrings by the sciatic nerve. The fibres which supply the extensor arise from the spinal nerve-roots which in man correspond to the 3rd and 4th lumbar; the hamstring supply is from the 5th lumbar and 1st and 2nd sacral roots.

Lombard's experiments upon the knee-jerk indicate that it is sometimes more readily obtained even in the same person than at other times. It varies with changes in mental activity, and during sleep may be entirely absent. It is increased and diminished by whatever increases or diminishes the relative state of irritability of the nervous system as a whole.

Closely related to this is the phenomenon known as *reinforcement of the knee-jerk*, which was first described by Jendrassik in 1883, and has since been studied by numerous observers. The extent of the jerk may be increased if at the time the patellar tendon is struck, a

* Sometimes known as the vastus crureus.

strong voluntary contraction, such as clenching the fists or the jaw, is made by the individual. In many normal persons the knee-jerk is difficult to elicit, but it must never be regarded as absent until reinforcement has been tried. After the reinforcing action has occurred it is followed by an interval in which the knee-jerk is lessened (inhibition or negative reinforcement).

Absence of Reflexes.—The tendon reflexes must obviously disappear if any part of the arc on which they depend is destroyed. Disease or injury of the afferent nerve, efferent nerve, or spinal grey matter, abolishes them. Thus they cannot be obtained in locomotor ataxy (damage to the posterior nerve-roots), or in infantile paralysis also known as anterior poliomyelitis (damage to the anterior horns of grey matter). This absence of the reflexes is therefore an important diagnostic sign of disease of the spinal cord or of the nerve-roots. Especially is this so if the tendon reflexes which are usually elicited are affected, but the superficial reflexes (see below) are more variable and may be unobtainable even in the absence of nervous disease.

Alteration of the Character of the Reflex.—This is well seen in the case of the knee-jerk. In lesions of the pyramidal tracts as in the decerebrate animal the knee-jerk is too well sustained, but on the other hand in cerebellar disease the leg falls quite limply. The normal is midway between the two. These facts indicate that the knee-jerk is intimately related to higher mechanisms. It is indeed a fractionated stretch reflex or part of the more complicated reflex by which we stand (see Mid-Brain Animal).

The Influences of the Higher Centres on Lower Reflex Arcs.—If, in the frog experiments referred to on p. 585, the cerebrum only is destroyed and the optic lobes left intact, the reflex reactions are found to be appreciably slower, thus showing the inhibitory effect of the remaining parts of the brain.

In man, this influence is of considerable clinical importance in the diagnosis of nervous disease, in which an **exaggeration of the reflexes** may, in certain circumstances, be considered to indicate that the higher centres have been cut off, *e.g.*, by damage to the motor tracts. The state thus produced is that of the chronic spinal animal in which the shock of the operation has passed off. Research suggests that the exaggeration is essentially the result of the cutting off of the impulses which pass down the rubrospinal tracts, but as these tracts lie in close association with the pyramidal tracts in the cord, conditions which affect one tract commonly affect the other. The reflex may be exaggerated in any condition which increases the irritability of the nervous system.

The effect of reinforcement referred to above is a closely allied

phenomenon, but a generally accepted explanation has not yet been found. On the other hand, we are familiar with the fact that reflexes may be largely inhibited by volition, *e.g.* sneezing. Cranmer, when burnt at the stake, held his hand in the fire till it was consumed.

The Plantar Reflex.—We have seen in the frog experiment described above that two reflexes may be produced by stimulation of the foot. Two similar reflexes are seen in man: the *withdrawal reflex*, involving fanning of the toes and dorsiflexion of the great toe (extensor plantar response); and the *thrust reflex*, involving flexion of the toes (flexor plantar response). Normally they are elicited by two distinct varieties of stimulation, but, as a result of walking, the protective withdrawal reflex is in partial abeyance and a *gentle* scratch of the sole of the foot with the finger-nail causes flexion of the toes. In disease of the pyramidal tracts, however, or in very deep sleep, whether normal or produced by a narcotic, when local protection is more essential, the withdrawal reflex is more prominent and such stimulation causes extension of the toes, especially the great toe. This is an important diagnostic sign of interference with the pyramidal tract (Babinski's sign); or, in some persons it may appear in excessive fatigue as occurs after long marches. This may be the result of fatigue of the higher centres. American workers have put forward evidence that the fanning component is the result of interference with the extra-pyramidal system from the red nucleus. (See Fulton.)

The Relation of Reflexes to Muscle Tone.—Commonly, changes in the reflexes are associated with alterations in muscle tone which we know to be a reflex phenomenon, but for convenience this is considered separately.

The Superficial Reflexes.

These reflexes are probably protective in nature. They are obtained by a gentle stimulation, such as a touch on the skin; the muscles beneath are usually affected, but muscles at a distance may be affected also, for example:

a. *Gluteal reflex*: a contraction in the gluteus when the skin over it is stimulated.

b. *Cremasteric reflex*: a retraction of the testicle when the skin on the inner side of the thigh is stimulated.

c. *Abdominal reflex*: a contraction of the muscles of the abdominal wall when the skin over the side of the abdomen is stroked; the upper part of this reflex is a very definite contraction at the epigastrium, and has been termed the *epigastric reflex*.

d. A series of similar reflex actions may be obtained in the muscles of the back, the highest being in the muscles of the scapula.

These reflexes commonly disappear if the pyramidal tracts are destroyed, but they are so variable normally that little is known regarding the exact pathways on which they depend. In animals some of them appear to play a part in the driving off of flies.

The Visceral Reflexes.

The spinal grey matter contains centres which regulate the operation of many involuntary muscles. Some of these centres are:—

The *cilio-spinal* centre which controls the dilatation of the pupil; it is situated in the lower cervical region, reaching as far down as the origin of the first to the third thoracic nerve.

Subsidiary *vasomotor* centres. The principal vasomotor centre is situated in the bulb, and subsidiary centres are scattered through the spinal grey matter.

Centres probably exist for all the muscular viscera, but particular study has been directed to those in the pelvis, and centres for *micturition*, *defæcation*, *erection*, and *parturition* are contained in the lumbo-sacral region of the cord. If the spinal cord is cut through above the situation of these centres, the result is, in general terms, that any influence of the higher (voluntary) centres over these actions is no longer possible. The actions in question are then simply reflex ones occurring after a period of shock (see Micturition) unconsciously at certain intervals, and set in movement by the peripheral stimulus (distension of bladder, of rectum, etc.).

The phenomena of micturition and defæcation have, however, already been described at length.

Muscle Tone and the Postural Reflexes.

In our consideration of the tendon reflexes we saw that certain reflexes occur when tendons are stretched by tapping or otherwise. These reflexes are, however, really part of a most elaborate mechanism by which the body maintains its posture and co-ordinates its muscular activities. The so-called "stretch reflex" is therefore of fundamental importance in the maintenance of posture.

Normally the muscles of the body, even when apparently at rest, are not fully relaxed, but are constantly maintained in a state of partial contraction. This state we know as **tonus**.

This may readily be seen in a decerebrate frog, which, if held up by the head, is seen to maintain its legs in a slightly flexed position. If, however, the anterior or posterior lumbar roots are cut, or the spinal cord in the lumbar region destroyed, the legs hang flaccid. It is evident from such experiments that the muscular tone which

was present was dependent not only on impulses which pass out from the cord but also on those which pass in by the posterior roots. Similarly, in man, if any condition is present which interferes with the spinal arc, either on the afferent or the efferent side, there is unusual flaccidity. On the other hand, if the pyramidal tracts are destroyed by disease there is found in association with the increased reflexes a marked rigidity of the lower limbs due to increased tone of the extensors. Generally we may say that loss of reflexes is associated with loss of tone and increase of reflexes with increase of tone. (Cobb, 1925.)

We may arrive at some, as yet incomplete, explanation of these facts if we study the phenomenon of muscle tone in animals.

The Spinal Animal has already been studied (p. 585). It has been seen that it is possessed of flexor tone and that it shows an exaggeration of the protective flexor reflexes, and may, after a period of absence, also show tendon reflexes. (See fig. 197, p. 600.)

The Mid-Brain Animal.—If, however, the section is made through the mid-brain, through or just below the red nucleus, quite the opposite state of affairs is produced, namely, that first described by Sherrington as **decerebrate rigidity**, which is a state in which there is gross exaggeration of the antigravity reflexes. The condition has been much studied because of the light it throws on the mechanism of posture generally and on states of rigidity which occur in disease in man.

The Nature of the Rigidity.—Fundamentally the rigidity is due to a sustained exaggeration of the antigravity extensor reflexes already described and the result of stimuli which originate in the stretched tendons and muscles, which normally extend the limb. In this condition the limbs are fully extended and are rigid as the result of increased tone in the muscles of the back and neck in the quadriceps, the extensor of the knee, and in the gastrocnemius at the back of the leg. There is produced, in other words, a condition of reflex standing, since all the anti-gravity muscles are contracted and the preparation can therefore maintain its own weight if placed on its feet, but cannot right its position if pushed over. The reflex paths concerned in the phenomenon may be investigated by studying the condition of the tone present in the quadriceps extensor of the knee. It is found that the maintenance of the tone depends on both the anterior and posterior roots (lumbar 5 and 6 in the case of the quadriceps in the cat), indicating that tonus is dependent on afferent impulses arising in the muscle itself. These impulses may be shown to depend on the slight stretch imposed on the muscle by its bony attachments from the tendency for the legs to bend, since, if the tendon is severed, the tonus and the impulses which are found by the

electrical method to pass up its nerve at the rate of 15 per second at once disappear. Nor is the cerebellum concerned for it can be removed without affecting the rigidity. That the skin is not involved is seen by the fact that decerebrate rigidity is fully present in a skinned limb. Impulses from the labyrinth are concerned in the neck and forelimb rigidity.

The Central Mechanism Involved.—It is seen, however, that the central nervous system, as high as the pons, is concerned in the

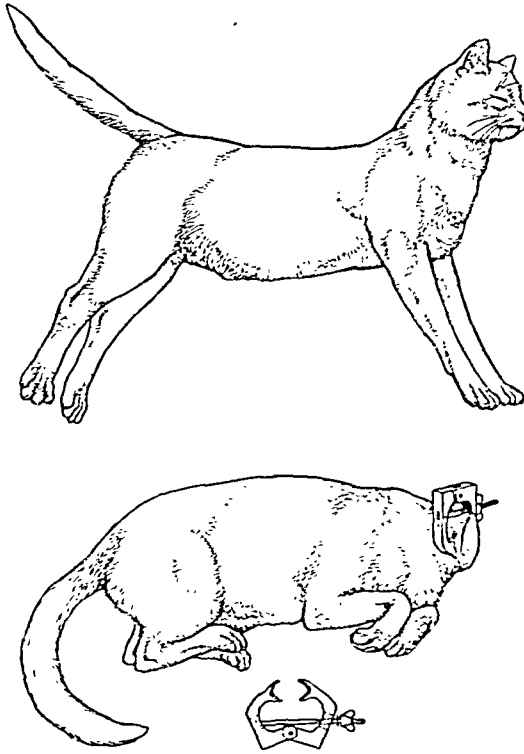


FIG. 197.—The upper drawing shows the posture of a mid-brain animal in decerebrate rigidity. The lower shows the posture of a spinal cat. A clamp (McDowall) is applied to the vertebral arteries, the carotid arteries being occluded. Artificial respiration is needed.

reaction, since destruction of Deiters' nucleus or section of the antero-lateral tract removes the rigidity. Thus we may conclude that this condition of decerebrate rigidity depends on a reflex arc, of which the afferent side is the afferent nerves from the muscles, the posterior roots, and the antero-lateral tract, while the efferent side is the vestibulo-spinal tract from Deiters' nucleus (Bazett) in the upper medulla and lower pons, the anterior roots and the motor nerves to the muscles.

Normally it would seem that decerebrate rigidity is essentially a release phenomenon; that is, the reflex arc upon which it depends is released by the section from the influence of the higher centres.

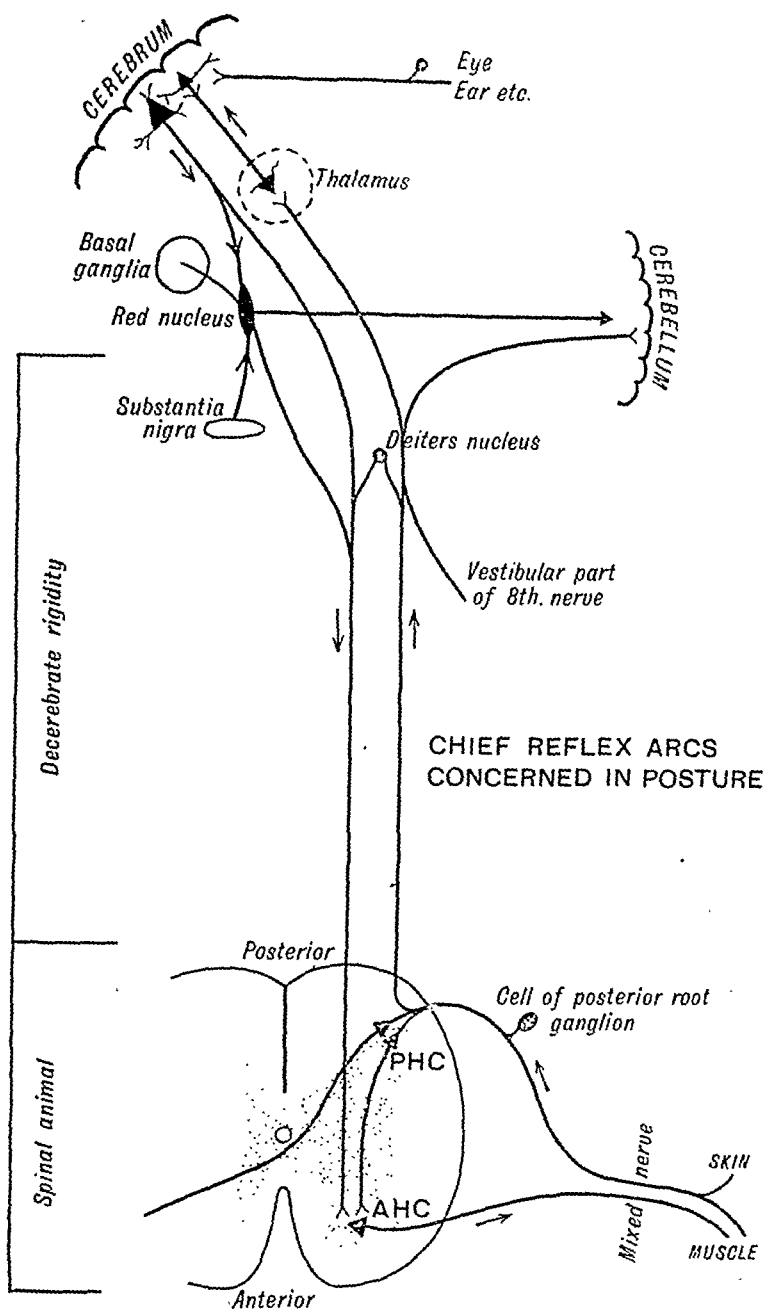


FIG. 198.—The lower part of the figure shows a simple spinal reflex arc and the reflex pathways of the spinal animal. The upper part shows the arc responsible for decerebrate rigidity and the sources of the impulses from the red nucleus and the cerebrum which inhibit it. For convenience the vestibulo-spinal and rubro-spinal tracts are shown as fusing; also only one neurone is shown joining PHC and AHC. The sensory fibre entering the cord is shown dividing. The three branches are distributed to the cells in the posterior root ganglion. Probably there is a chain of internuncial neurones with lateral connections at this point.

The higher centres concerned are the red nucleus and probably the cerebrum, for it has been found that careful destruction of the red nucleus only (Ranson) or section of the rubro-spinal tracts does

not cause rigidity unless the pyramidal tracts are also cut, while stimulation of the latter causes the rigidity to disappear (see fig. 198). Animals in which the cortex has been removed tend, too, to have some extensor rigidity, although the distribution of tone is fairly normal (Bard). It would seem then that impulses which travel down by the rubro-spinal and the pyramidal tracts compete with those from the vestibulo-spinal tracts for effects on the anterior horn cells of the spinal cord.

In man, states similar to decerebrate rigidity are met with in tumours involving the mid-brain and pyramidal tracts, but the legs, for various reasons, are more affected than the arms, which, indeed, may be flexed (see Cortical Flexion, below). In meningitis a condition almost identical with decerebrate rigidity may sometimes be seen; in this, retraction of the head is a marked feature.

In the cat it is easy to demonstrate the conversion of a decerebrate animal into a spinal animal by clamping the vertebral and carotid arteries. This procedure destroys Deiters' nucleus which, however, recovers again if the carotid is released. It is thus possible to flex and extend the legs by clamping and releasing the carotid artery. Experimentally, decerebrate rigidity is absent if carbon dioxide is washed out by over-ventilation.

The Characteristics of the Rigid Muscles.—The contraction is a sustained contraction especially of the red fibres in muscle (p. 15). It must then be looked upon as a form of tetanus which results from slow periodic discharges of certain motor cells acting cyclically. It must be understood that the amount of muscular tension thus kept up is only a fraction of the maximum which can be produced by the same muscles, and the amount of oxygen required is only 25 per cent. above that required at rest. The liability to fatigue is, therefore, very little indeed; the rigidity can be kept up for many days. The reflexes are very resistant to inhibition and their rate of electrical discharge is very slow—5 to 8 per second. The posturing limb shows the phenomenon of *plasticity*, which tends to keep the limb in whatever position it is placed.

The degree of tone in posturing muscles is related to the body as a whole (see tonic reflexes below).

Reflex walking may be seen if a roller platform is moved along the feet of a suspended decerebrate animal; if the movement is rapid the carcass gallops, if slow it walks. (Graham Brown.)

An interesting phenomenon of posturing muscle is the *lengthening reaction*. If the muscle is severely stretched it is felt to give way owing to a sudden disappearance of the tone as a result of inhibitory impulses which pass up from the muscle spindles. This reaction, together with fractionation, is important in preventing the tearing of muscles. It seems likely that the excessive strength of lunatics

and of athletes trained for specialised events somehow have the lengthening reaction reduced.

The Thalamic Animal.—If a section is made above the red nucleus, the postural reactions and balance of the animal are complete. For convenience the thalamus also is left intact in order that the animal shall be able to regulate its own body temperature. The animal possesses *righting reflexes*, that is, is capable of righting itself from any position in which it may be placed, although of course by the removal of the cerebrum it is deprived of all volition and is a mere automaton. It can also walk about, but it does so stiffly because of the presence of the slight exaggeration of tone in the extensor muscles, due to some release of the antigravity reflexes. If the animal is suspended there is an extensor rigidity not depending on stretch reflexes (Bard and Rioch).

Experiments on the decerebrate and thalamic animal, which we owe largely to the schools of Magnus in Utrecht and of Sherrington in Oxford, show that certain parts of the body bear a definite relation to each other in the maintenance of posture, and that when one part of the body is moved, a reflex alteration in tone changes the position of other parts of the body. Thus, if the neck is flexed, the fore legs bend and the hind legs extend, while the opposite occurs if the head is extended (*i.e.* a *tonic neck reflex* occurs). Such movements, it is realised, take place together normally in the life of the animal when it is eating or looking up. Also if one leg is bent the other may extend as in walking. This is known as the *crossed extension reflex*. Similarly, if the head is turned to one side the limbs on that side show increased extensor tonus as if to support the weight of the body while the tonus of the opposite side decreases.

Thus we see that the central nervous system, as high up as the thalamus, is possessed of a very large degree of reflex activity which automatically promotes the interests of the animal.

Cortical Flexion.—As an animal comes out of certain anaesthetics, *e.g.* avertin and sometimes ether, it develops typical decerebrate rigidity. This, however, gives way to a flexor rigidity which is seen in the fore-limbs before the hind-limbs. It has been shown that this rigidity depends on the cerebral cortex, since it is absent if the cortex is removed (Blair and McDowall). The state is so like that present in a spinal animal that it may be suggested that it represents a group of higher protective reflexes. The phenomenon is important as it is so similar to the state of flexed fore-limbs and extended hind-limbs seen in cerebral hæmorrhage in man. The so-called convulsions which occur occasionally during ether anaesthesia may be also similarly produced.

The Maintenance of Posture.

The facts which have been given above show quite definitely that the maintenance of posture is purely a reflex phenomenon which does not involve the cerebrum or conscious effort. The experiments given above suggest that the muscular reflexes with which the nervous system of the elementary spinal animal is concerned are those of protection of the animal. With the greater development of locomotion are developed the antigravity reflexes which are exhibited by the decerebrate animal. Such extensor reflexes have arcs through the medulla and pons. They do not, however, depend, as used to be thought, on the cerebellum. Normally, however, these extensors appear to be held in check by a still higher set of reflexes involving the mid-brain. In the higher mammals this part of the brain is quite small, but in lower animals, especially those who have to maintain posture in vertical as well as horizontal planes, *e.g.* birds and fishes, the so-called optic lobes of the mid-brain are more conspicuous than any other part of the brain. These are represented in the mammal by the corpora quadrigemina, which are quite small.

Muscular Co-ordination and the Maintenance of Equilibrium.—Although posture and equilibrium are closely allied phenomena they are not quite identical. Equilibrium includes the maintenance of posture, but involves also maintenance of steadiness during muscular movement, such as walking. In this, the maintenance of proper co-ordination of muscular activity is essential. The reflexes concerned are very similar to those of posture, but, apparently, normally they involve to a greater extent the cerebellum and the semicircular canals.

Receptors and Reflexes concerned in Posture and Equilibrium.

The afferent impulses originate from the following four sources:—skin; joints and muscles; retinae; labyrinths.

In the accurate investigation of these reflexes decerebrate animals are used for the tonic postural reflexes, and thalamic animals (p. 603) for the righting reflexes. When one kind of receptor is being investigated it is necessary to exclude the others, *e.g.* by blindfolding, by removing the labyrinths, or by immobilising muscles.

1. **The Skin.**—Sherrington has shown how comparatively unimportant is the loss of tactile sensibility from the feet. A cat, in which the feet have been completely desensitised by division of nerves, can stand and walk without obvious inconvenience.

It has been shown, however, by Rademaker that certain *body righting reflexes* which tend to bring the body from the lateral to the normal position have their origin in the skin.

2. The Muscles and Joints.—We have already seen that stretching or tapping of a muscle may originate nerve impulses. This occurs from the stretching or compression of the specialised nerve-endings, the tendon organs, and muscle spindles. The shortening reaction appears to depend on the tendon organs (Denny Brown) which, however, are not confined to the tendons as originally thought, while the lengthening reaction depends on the spindles. The spindles give rise to impulses by which we become aware of the movement and position of our muscles, but in this connection we are concerned with those impulses which do not reach consciousness. The fibres which carry the latter are off-shoots of the sensory fibres and reach the mid-brain and cerebellum *via* Clarke's column and the cerebellar and tecto-spinal tracts.

The reflexes which are set up are known as tonic and righting reflexes, which may arise from the muscles of the body or the neck. Some cause the body to follow the head (*neck righting reflexes*), others (*tonic neck reflexes*) cause a change in tone in certain muscles (p. 603) in accordance with the requirements of the head.

The difficulty experienced by quite normal persons in standing on one leg with the eyes shut, is due to a reduction of the number of these impulses, for the same subjects with the eyes shut can stand quite easily on both legs; displacement of the centre of gravity, caused by standing on one leg, must however be taken into account. In many cases of tabes* there is but little loss of tactile sensibility, and the condition of inco-ordination is chiefly due to the loss of impressions from muscles and joints. In these cases, however, the sense of equilibrium is not lost; the man realises that he is unsteady.

3. The Retinæ.—The eyes are important sensory receptors in relation to posture and equilibrium.

They are the receptors of the *optical righting reflexes*. It can be shown that if a labyrinthectomised monkey be blindfolded and suspended in any position it makes no attempt to right itself, but does so as soon as the bandage is removed. The centres for such reflexes are in the occipital cortex.

The importance of the retinæ is increased when the other receptors are interfered with. This is well illustrated by the case of the tabetic who has deficient joint and muscle sense due to disease of the posterior nerve-roots; the visual postural reflexes have become educated to replace the diminished reflexes from the muscles, and directly the individual is deprived of them he becomes unsteady or even falls. This phenomenon is known as Romberg's sign. Since, however, the labyrinths are normal the subject is quite aware of his unsteadiness.

As has been indicated above, the capability of an individual to stand on one leg depends, to a considerable extent, on impulses from the eyes. In some individuals the paralysis of accommodation by the instillation of atropine into the eyes causes interference with

* See footnote on p. 594.

the maintenance of posture. This suggests that the actual focusing of objects is of special importance.

Bandaging of the eyes in animals often causes them to spin round and lose their balance. The giddiness experienced by many people on looking from a height or at moving water, or after the onset of a squint, or when objects are viewed under unusual circumstances, as in the ascent of a mountain railway, is due to the same thing. It should be understood that visual impressions in themselves are not the sole guide. It is the projection of what is seen in relation to the position of the body (ascertained by the innervation of the neck muscles and of the ocular muscles) which is the chief guide.

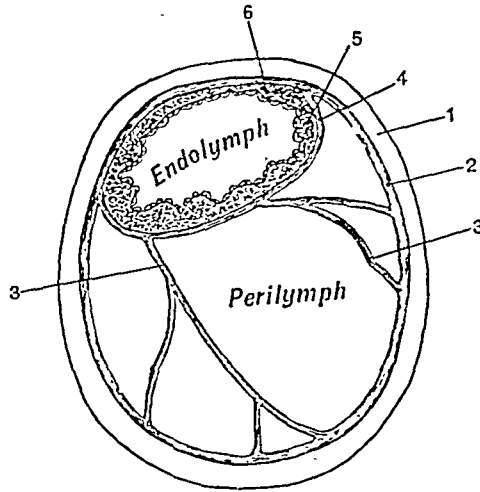


FIG. 190.—Section of human semicircular canal. (After Rüdinger.) 1, Bone; 2, periosteum; 3, 3, fibrous bands connecting the periosteum to 4, the outer fibrous coat of the membranous canal; 5, tunica propria; 6, epithelium.

4. **The Labyrinth.**—An external view of the labyrinth, which is enclosed within the petrous portion of the temporal bone, is shown in fig. 245, p. 718. The labyrinth consists of three parts—the vestibule (1), the three **semicircular canals** (3, 4, 5) which open into the vestibule, and the tube, coiled like a snail's shell, called the cochlea (6, 7, 8). The cochlea is the part of the apparatus which is concerned in the reception of auditory impressions; it is supplied by the cochlear division of the eighth or auditory nerve. The remainder of the internal ear is concerned not in hearing, but in the reception of the impressions we are now studying; it is supplied by the vestibular division of the eighth nerve. Within the vestibule are two chambers made of membrane, called the **utricle** and the **saccul**e; these communicate with one another and with the canal of the cochlea (see Hearing). Within each bony canal is a membranous canal of similar shape. Each canal is filled with a watery fluid called *endolymph*, and separated from the bony canal by another

fluid called *perilymph*. Each canal has a swelling at one end called the *ampulla*. The membranous canals open into the utricle: the *horizontal* canal by each of its ends; the *superior* and *posterior* vertical canals by three openings, these two canals being connected at their non-ampullary ends.

Fig. 199 shows in transverse section the way in which a membranous canal is contained within the bony canal; the membranous canal consists of three layers: the outer-layer is fibrous and

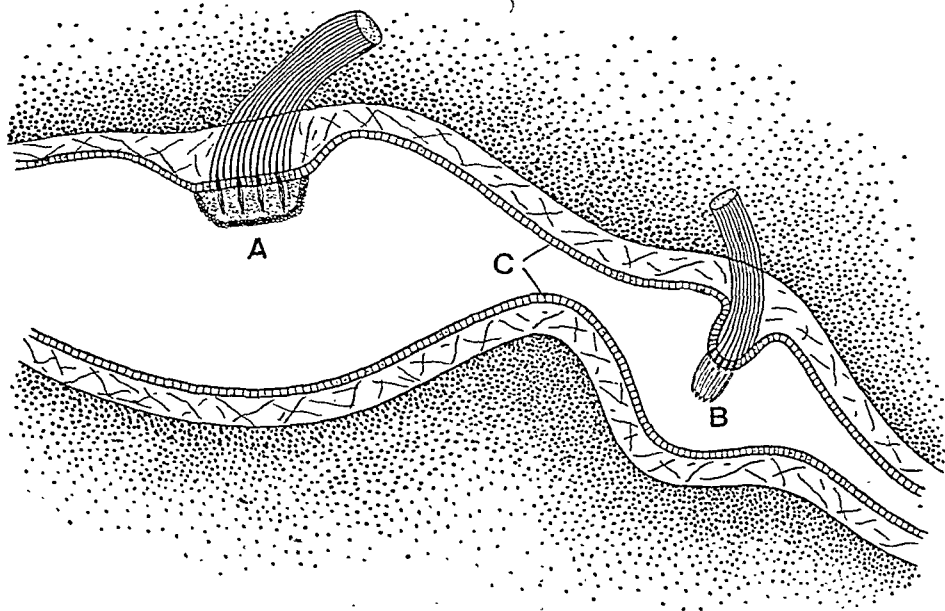


FIG. 200.

continuous with the periosteum that lines the bony canal; then comes the *tunica propria*, composed of homogeneous material, and thrown into papillæ except just where the attachment of the membranous to the bony canal is closest; the innermost layer is a somewhat flattened epithelium.

At the ampulla there is a different appearance; the *tunica propria* is raised into a hillock called the *crista acustica* (see fig. 200); the cells of the epithelium become columnar in shape, and to some of them fibres of the eighth nerve pass, arborising round them; these cells are provided with stiff hairs, which project into what is called the *cupula*, a mass of mucus-like material. Between the hair-cells are fibre-cells which act as supports. When the pressure of the endolymph in the interior of the canals is altered, the hairs of the hair-cells are affected, and a nervous impulse is set up in the contiguous nerve-fibres, which carry it to the central nervous system. The stimulation of the hairs is brought about by the movements of the endolymph.

The Function of the Otolithic Cavities.

Since the position of the head is of such importance in maintaining posture, a special mechanism has been developed with the utricle and saccule* which is affected by gravity and in which impulses are set up which are carried to the brain also by the vestibular nerve.

In each saccule and utricle is the macula, resembling in structure the cristæ acusticæ of the semicircular canals (p. 61) but in addition there are entangled in the hairs of the hair-cells calcareous bodies known as *otoliths*, which stimulate the hairs by pulling. The function of an otolithic cavity was first discovered in the crayfish, whose cavity is open to the exterior and which replaces the otoliths periodically by grains of sand; when Kreb replaced the sand by iron filings and approached the animal with a magnet, the animal could be made to turn somersaults or to adopt any position, according to the direction of pull of the magnet. In the mammal, definite alterations in the tone of muscles are caused by change in position of the head, even when the reflexes due to stretching of the neck muscles are excluded by fixing the neck in plaster of Paris. The reflexes from the labyrinths have a longer latent period than those from the neck; the effects from the neck and labyrinth are summated.

The reflexes are of two categories: (1) *tonic labyrinthine reflexes* which are shown by the decerebrate animal and which relate the position of the body and limbs to that of the head. These depend on the utricle whose otoliths lie above the horizontal maculæ, and (2) *labyrinthine righting reflexes* which are shown by the thalamic animal and which are concerned with maintaining the head in its normal position in relation to the earth's surface. If the body is moved in such an animal the head is automatically righted. The asymmetric righting reflexes depend on the saccules whose otoliths lie lateral to the vertical maculæ; the symmetrical righting reflexes arise probably in both utricles and saccules.

After bilateral destruction of the labyrinth an animal soon recovers from the effect of the operation, because of its visceromotor postural reflexes; but certain functions are never recovered. The cat, for example, never regains its proverbial power of falling on its feet if thrown from a height, and ceases to be able to rise to the surface and swim when thrown into water.

The function of the otolithic cavities only may be destroyed by centrifuging the animal, a procedure which causes it to be unable

* There is some evidence that the saccule is chiefly concerned with appreciation of coarse vibration.

regain its posture, but it may still respond to some extent to sudden movement of the head as the semicircular canals act normally. The otolithic cavities may then be looked upon as the organs of static equilibrium.

The vestibular nerve arises from the bipolar cells of the *ganglion of Scarpa*, which is situated in the internal auditory meatus. The peripheral axons ramify among the hair-cells of the epithelium in the utricle, saccule, and semicircular canals. The central axons enter a collection of small nerve-cells between the restiform body and the descending root of the fifth; this is termed the *principal nucleus*; here they bifurcate; the descending branches run towards the lower part of the bulb, and arborise round the cells of the neighbouring grey matter (descending vestibular nucleus). The ascending branches pass upwards, some to the cerebrum, but most by the restiform body to the cerebellum; in their course they give off many collaterals which form synapses with the cells of two nuclei near the outer angle of the ventricular floor, known as the *nucleus of Deiters* and *nucleus of Bechterew*. The fibres which arise from Deiters' nucleus pass into the posterior longitudinal bundles of both sides; those which start in *Bechterew's nucleus* become longitudinal, but their destination is uncertain.

The Function of the Semicircular Canals.

It will be noticed that the canals on each side are in three planes at right angles to each other, and we learn the movements of the head with regard to the three dimensions of space by means of impressions from the ampullary endings of the vestibular nerve; these impressions are set up by the varying pressure of the endolymph in the ampullæ.

Thus a sudden turning of the head from right to left will cause movement of the endolymph towards, and therefore increased pressure on, the hair-cells connected to the ampullary nerve-endings of the left horizontal canal, and diminished pressure on the corresponding apparatus of the right side. It is probable that resulting from such a movement two impulses reach the brain, one the effect of increased pressure in one ampulla, the second the effect of decreased pressure in its fellow. It may even be that increased pressure on one side of a crista is accompanied by diminished pressure on the opposite face of the same crista.

"One canal can be affected by, and transmit the sensation of rotation about one axis in one direction only; and for complete perception of rotation in any direction about any axis, six canals are required in three pairs, each pair being in the same or parallel planes, and their ampullæ turned opposite ways. Each pair would thus be sensitive to any rotation about a line at right angles to its plane or planes, the one canal being influenced by rotation in one direction, the other by rotation in the opposite direction." (Crum-Brown.)

The two horizontal canals are in the same plane; the posterior vertical of one side is in a plane parallel to that of the superior vertical of the other side (see fig. 201).

When these canals are diseased in man, as in Menière's disease, there are disturbances of equilibrium: a feeling of giddiness, which may lead to the patient's falling down, is associated with nausea and vomiting. In animals similar results are produced by injury, and the subject has been chiefly worked out on birds by Flourens, where the canals are large and readily exposed, and in fishes by Lee.

Thus, if the horizontal canal is divided in a pigeon, the head is thrown into a series of oscillations in a horizontal plane, which are increased by section of the corresponding canal of the opposite side. After section of the vertical canals, the forced movements are in a vertical plane, and the animal tends to turn somersaults.

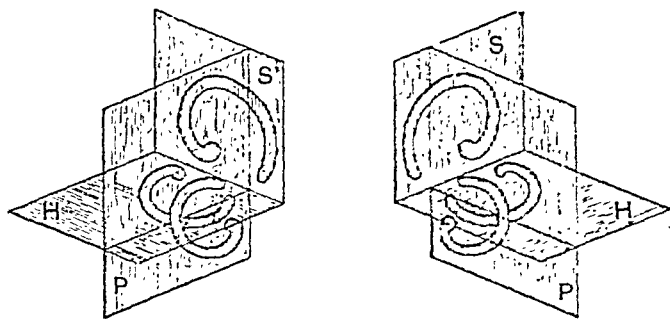


FIG. 201.—Diagram of semicircular canals, to show their positions in three planes at right angles to each other. It will be seen that the two horizontal canals (H) lie in the same plane: and that the superior vertical of one side (S) lies in a plane parallel to that of the posterior vertical (P) of the other. (The student will understand that, though in the diagram the canals are entirely separated from one another, they are really connected.) (After Ewald.)

“When the whole of the canals are destroyed on both sides the disturbances of equilibrium are of the most pronounced character. Goltz describes a pigeon so treated which always kept its head with the occiput touching the breast, the vertex directed downwards, with the right eye looking to the left and the left looking to the right, the head being incessantly swung in a pendulum-like manner. It can neither stand, nor lie still, nor fly, nor maintain any fixed attitude. It executes violent somersaults, now forwards, now backwards, rolls round and round, or springs in the air and falls back to recommence anew. It is necessary to envelop the animals in some soft covering to prevent them dashing themselves to pieces by the violence of their movements, and even then not always with success. The extreme agitation is manifest only during the first few days following the operation, and the animal may then be set free without danger; but it is still unable to stand or walk, and tumultuous movements come on from the slightest disturbance. After the lapse of a fortnight it is able to maintain its upright position. At this stage it resembles an animal painfully learning to stand and walk. In this it relies mainly on its vision, and it is only necessary to cover

the eyes with a hood to dispel all the fruits of this new education, and cause the reappearance of all the motor disorders." (Ferrier.)

It is these canals which enable the individual to know in which direction he is being moved, even though the eyes are bandaged, and the feet are not allowed to touch the ground. On being whirled round, such a person knows in which direction he is being moved, and feels that he is moving so long as the rate of rotation varies, but when the whirling stops he seems, especially if he opens his eyes, to be whirling in the opposite direction, probably owing to the rebound of the fluid in the canals. The forced movements just described in animals are due both to the absence of the normal sensations from the canals and to delusive sensations arising from their irritation, and the animal makes efforts to correct the movement which it imagines it is being subjected to.

It has been found possible by Adrian to record from the vestibular nucleus impulses set up by movement of the semicircular canals. A canal appears to be stimulated by movement in one direction only, but sometimes a resting discharge has been recorded which is abolished by movement in the other direction.

The impulses which co-ordinate reflex movements of the head, neck and eyes are carried by the posterior longitudinal bundle which connects the nuclei of the cranial nerves with each other and the anterior horn cells of the spinal nerves.

The semicircular canals are then essentially the organs for the maintenance of dynamic equilibrium. There is some evidence that the semicircular canals may take a greater part in maintaining static equilibrium than has hitherto been supposed, and in support of this it has been found photographically that in the standing position there is usually, if not always, a swaying movement of the head. (Magnus, Camis.)

LOWER NERVOUS MECHANISMS INVOLVED IN CO-ORDINATED MOVEMENTS.

It will be understood that such mechanisms are not confined to the spinal cord but are concerned in the activities of those parts of the brain-stem which control the muscles of the head. A fuller description is given by Creed, Denny-Brown, Eccles, Liddell, and Sherrington, 1932.

Reciprocal Innervation of Antagonistic Muscles.—When a muscle is stimulated reflexly so as to flex a joint it is evident that the extensor muscles must at the same time become elongated. This elongation is not a passive phenomenon but is an active relaxation of the muscle which, as we have noted on page 598, is

always in a state of tonus or partial contraction. This may be shown experimentally by separating, say, the tendons flexing and extending the knee-joint and attaching them to levers. The levers must be sufficiently weighted to stretch the muscle so that their tone may be kept up reflexly by the stretch reflex or shortening reaction (p. 586). If, then, the knee is caused to be flexed by stimulating an afferent nerve of the opposite side it will be found that there is a lengthening of the extensor muscle. Thus there is, as first shown by Sherrington, reciprocal action between the flexors and extensors. There is, however, a very marked degree of grading between the

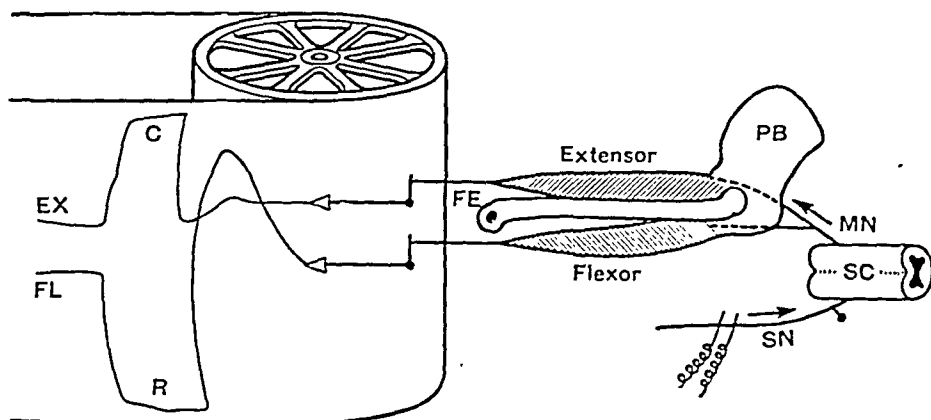


FIG. 202.—Diagram to illustrate reciprocal innervation. The flexor and extensor muscles of the thigh are attached to levers as indicated and the femur FE and the pelvic bone PB firmly held. When a sensory nerve of the opposite side is stimulated the extensor contracts but the flexor relaxes.

two activities. According to Graham Brown the sum of the relaxation and the contraction is equal, the relaxation being graded to the contraction by some central mechanism. (See fig. 202.)

In every voluntary act there is this reciprocal contraction and relaxation of antagonistic muscles. In some persons the relaxation of the deltoid muscle can be felt if the elbow is supported on the arm of a chair and the limb is actively pressed against the side.

Sometimes this reciprocal arrangement gets thrown out of gear. This occurs in strychnine poisoning and in lockjaw. When the unfortunate patient tries to open his mouth the stronger muscles which ought to relax contract at the same time and the jaw is fixed. Death occurs from asphyxia because the respiratory muscles go into spasm and fix the thorax as a result of the failure of the reciprocal mechanisms.

It is suggested by Gasser (1937) that the inhibition is produced at certain cells by very rapidly travelling impulses which are capable of producing a subnormal phase such as occurs in peripheral nerve (see Refractory Phase of Nerve). (See also p. 615).

Of course by volition it is possible to contract flexors and extensors simultaneously.

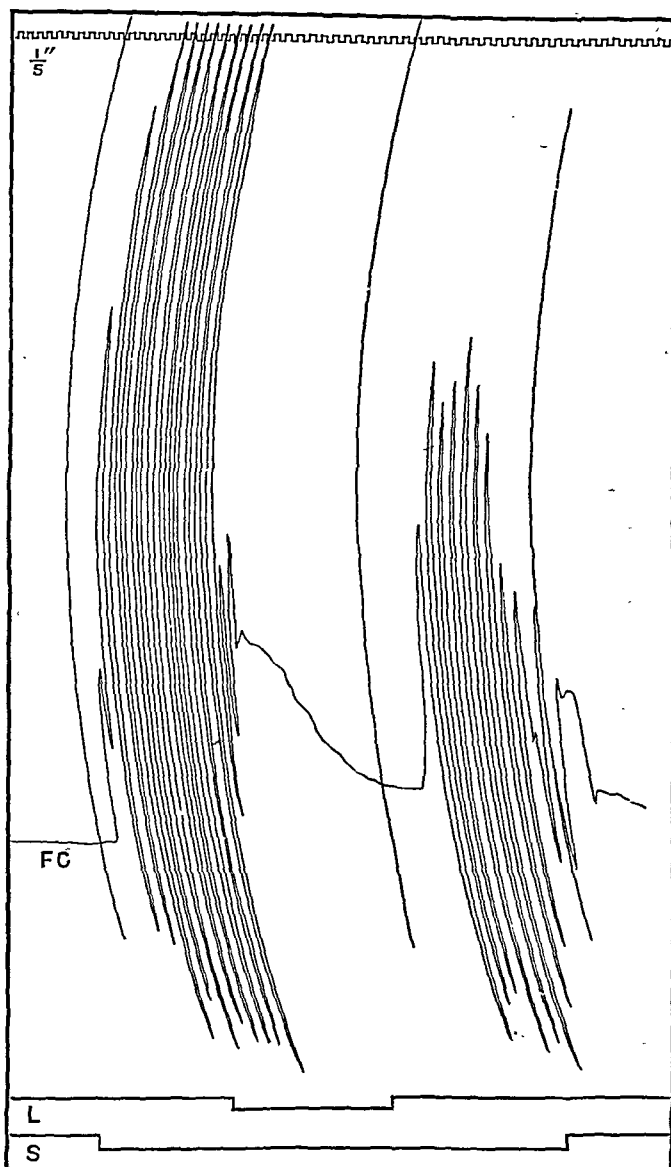


FIG. 203.—The scratch reflex. Tracing of the flexors of left hip evoked by stimulation of the skin of the shoulder. The depression in the signal line S indicates the commencement of the stimulation, and its rise the termination. While this was going on, the left foot was stimulated, and the depression of the signal line L indicates the duration of this stimulation; during the stimulation of the foot, and for a short time afterwards, the scratch reflex is inhibited, but the scratch reflex returns soon afterwards. The time is registered in fifths of seconds. To be read from left to right. (Sherrington.)

The Principle of the Common Path and of Convergence.—When a muscle is made to contract reflexly the impulse which starts at the point of stimulation uses a path which can only be used by

similar impulses arising from a given region of the body. It is a private path. When, however, the impulse reaches the spinal cord it uses paths used by impulses from other regions, and when it reaches the anterior horn cells through which it is finally effective it is said to use the *Final Common Path* from the motoneurone pool (p. 593). This is a public path upon which all impulses intended to reach any given muscle must converge. Upon this path converge not only afferent impulses arising from the periphery but the impulses which arise in the higher parts of the brain and are concerned in voluntary activity.

It is evident that occasions must arise in which there is competition, as it were, for the final common path.

For the investigation of such a problem, the "*scratch reflex*" of the dog is one that lends itself admirably. This can best be studied in the "spinal" dog, that is in a dog in which cerebral influence is shut off by division of the spinal cord in the lower cervical region. If the skin over a large saddle-shaped area covering the shoulders and back is gently scratched or stimulated with a weak faradic current on one side, the hind leg of the same side executes scratching movements, which involve flexor muscles principally. The scratch reflex is a movement by which an animal presumably rids itself of irritating insects.

When, however, the foot is stimulated the impulses set up, if noxious, take precedence in the final common path and the scratch reflex is inhibited (fig. 203).

The factors which are chiefly concerned in determining predominance in the final common path are (1) Strength of stimulus; (2) Importance of the stimulus in relation to survival; severe pain, for example, usually dominates. (3) Fatigue, however, reduces the power of dominance of a given stimulus.

The final common path is also used by a variety of reflexes, for in the language of the Oxford School "there is no reason to believe that the crossed extensor and the stretch reflex each possess a private motoneurone pool"; that is to say, the same groups of cells in the anterior horn of the spinal cord are used by a variety of stimuli arising from different sources.

Reinforcement.—Instances of reinforcing action may be found; for example, if two points of the skin of one shoulder are stimulated with a very feeble current, neither stimulus alone may be sufficient to evoke the scratch reflex, but the two together may elicit it; in order to attain this result the two points of skin must be fairly close together. Further detail is obtainable from Creed and others.

The Phenomenon of Excitation.

The problem of excitation in the central nervous system is similar to that of the excitation of a muscle by a nerve. We do not know whether it is essentially chemical or physical.

It is known that a central excitatory state can be built up by several sub-threshold stimuli which individually are insufficient to evoke a response. Moreover, the summation may be produced by the stimulation of different afferent nerves. Further, the application of one effective stimulus which has a central reflex time of 3-5 m. sec. reduces that of a second stimulus to 0.5 m. sec. provided the interval between the two is not more than 5-6 m. sec.

The Phenomenon of Inhibition.

Peripheral Inhibition.—This we have already noted in relation to the effect of the vagus on the heart, the inhibition of which is now known to be produced through the mediation of a chemical substance, acetyl-choline. Inhibition of the intestine by the splanchnic nerve is similarly brought about by the production of an adrenaline-like substance. How exactly these substances act is, however, unknown.

Central Inhibition.—As yet we have but fragmentary knowledge of this subject, but it is important not only in relation to spinal reflex but in relation to the higher reflexes which influence our social conduct. We have already discussed examples, *e.g.* the scratch reflex and reciprocal inhibition. Another is the crossed extension reflex (see p. 587). This may be brought about by stimulating the popliteal nerve of the opposite side at 48 per second when sustained contraction of the quadriceps occurs. Stimulation of a sensory nerve of the same side for even 0.3 sec. at once causes the contraction to cease, as seen in fig. 192.

This inhibition apparently takes place in the region of the anterior horn cells concerned and not on the sensory side of the arc, for cessation of the stimulus from the opposite side for a similar period (0.3 sec.) has no effect because of the after-discharge of the motor cells.

A central inhibition of the knee-jerk can also be produced and it can be shown that it is much easier to inhibit the knee-jerk of a spinal animal than that of a decerebrate animal.

In relation to conditioned reflexes below we shall see that whatever the nature of inhibition it is an active process, while the action of strychnine, which we have noted in relation to reciprocal innervation, suggests that it is a chemical process.

Many ingenious theories have been elaborated to account for existing facts, but so far each has fallen short when new facts have come to light. We are now doubtful whether peripheral and central inhibitions are such similar phenomena as appeared before the fact that nerves liberated chemical substances was discovered.

The extremely rapid action of the nervous system makes it difficult to imagine that the accumulation and disappearance of chemical substances are concerned. Yet all the available evidence indicates that changes of a physico-chemical nature take place.

It can, for example, be shown that when an afferent impulse reaches the motor cell of a reflex arc a **central excitatory state** is set up. It is capable of summation as a result of a succession of subminimal stimuli along the same afferent nerve, and when a certain degree of excitation has accumulated it discharges. There is evidence, however, that the discharge may vary in rate and it is suggested that muscle activity may be graded thereby. It is indeed possible to discharge the motor cell artificially by stimulating its axon and causing an impulse to pass up to the cell in the wrong direction. After-discharge can thereby be prevented (Eccles and Sherrington). The rate of discharge can be measured by recording the electrical variation of the muscle and the gradation of muscle activity (or the relative number of motor units thrown into activity) ascertained by finding the tension set up by the muscle.

It can be shown that there can in the same way be a summation of a **central inhibitory state**. This, however, is more persistent than C.E.S. (central excitatory state), and is not discharged by "antidromic" impulses.

As already mentioned, it has been suggested by Gasser that central inhibition is due to the production of a subnormal phase in motor cells such as occurs in peripheral nerve, and this view receives considerable support from the work of Eccles who, in studying the electrical response of ganglia, has shown that the occurrence of after-potential is related to the excitatory state as in the case of nerve-fibres. Details of this difficult subject are found in a review by Eccles (see references), but it will be seen that it is very difficult to reconcile this electrical view of excitability with that of chemical transmission at the synapses.

We must assume that in the delicate co-ordinated movements of which our muscles are capable and in which, as we have seen, the cerebellum, etc., are concerned, the mechanisms of excitation and inhibition are likewise intimately concerned.

Rhythmical Activity.

In many parts of the nervous system rhythmic activity is seen. The best known, perhaps, are those of the respiratory centres, the

scratch reflex just described, and that of stepping. In the case of the ankle clonus we have seen that it is dependent on tension on the calf muscles being maintained. Generally, however, the phasing of rhythmic movements is not caused by afferent stimuli, although they may regulate them, for they occur if the afferent pathways are cut. The rhythmicity depends on some inherent central mechanism not yet understood.

CONDITIONED REFLEXES.

In this variety of reflex we have the participation of the cerebral cortex and apparently of consciousness in its formation, and it is so called because it depends on training or conditioning for its establishment. Conditioned reflexes are not inborn, like the reflexes we have hitherto been considering, but have become acquired by the animal during its life-time. Our knowledge of these reflexes we owe largely to Pavlov, who has placed their study on an experimental basis. His classic experiment is well known. He showed that if a bell was rung each time food was given to a hungry dog, eventually the dog secreted saliva when it heard the bell although food was not presented. The showing of the food to the dog constitutes the *unconditioned stimulus*, the ringing of the bell the *conditioned stimulus*. The fact that a dog will secrete saliva when food is offered is well known, and may be looked upon as an inborn or unconditioned reflex; but it has now been shown that practically any stimulus not involving serious hurt to the animal, and provided it begins to act slightly before the normal activity, may, if it occurs simultaneously with the normal stimulus, become the conditioned stimulus. Even the cessation of a stimulus, *e.g.* of the ringing of a bell, may act as a stimulus. The sight of the syringe used for the injection of apomorphine is eventually sufficient to cause vomiting although no actual injection is made. Failure, however, to follow the conditioned by the unconditioned stimulus leads to weakening and eventually to *loss or extinction* of the reflex. Even allied reflexes are affected, a fact which indicates that the extinction is an active inhibitory process. A conditioned reflex may become established in relation to any reflex activity of the animal, even to the knee-jerk, but for the sake of simplicity most of the work has been carried out in relation to the secretion of saliva. For more accurate work the duct of a salivary gland is brought to the surface, so that the saliva can be easily collected and measured.

It is evident that in the formation of a conditioned reflex two processes occur, namely, an analysis of the stimulus which takes place in the cerebrum, which with the appropriate afferent nerve

and nerve-ending comprises the **analyser**, and an association of the conditioned and unconditioned stimulus. If the appropriate part of the cortex is removed, *e.g.* the temporal areas in a case in which the conditioned stimulus is a sound, the reflex disappears. This experiment is important, as it indicates that the reflex does not depend on any short-circuiting mechanism through lower centres as has been suggested.

Conditioned reflexes are of interest as they offer a method of investigation of the analysers and the power of the lower animals to differentiate between different kinds and intensities of stimuli; for example, it has been shown that a dog can differentiate between half tones on the piano. It has been possible also by their study to show that the power of localising the side from which a sound comes depends on integrity of the corpus callosum which joins the two cerebral hemispheres.

Conditioned reflexes show many of the characteristics of reflexes generally. Thus there may be *summation* from the addition of two conditioned stimuli. There may also be *spread*, but in this case it is in the area stimulated. If there is a localised conditioned stimulus from the skin, other near-by areas may subsequently give a similar response. Somewhat akin to this phenomenon is that of *linking*, in which it is found that if a reflex has become established to one sound it is much more easy to establish a second reflex from another sound.

Repetition plays a very important part in conditioned reflexes. It is not only necessary for the formation of the reflex but is essential for its maintenance, otherwise the reflex tends to *decay*. It is, however, readily *reinforced* by repetition of the procedure following up the conditioned by the unconditioned stimulus.

Conditioned reflexes are liable to be inhibited or stopped in certain circumstances. If, for example, an extraneous noise is heard this may cause a temporary **external inhibition** of the reflex. For this reason the animal is arranged in the special room indicated in the illustration and is observed indirectly through a system of mirrors or a periscope. If, however, the stimulus is harmful and affects the same region as the conditioned stimulus, the inhibition may be permanent. It is to be noted that the animals experimented upon are on the friendliest possible terms with the observers.

It has been found that a considerable interval may occur between the conditioned and the unconditioned stimulus, provided the former is applied first. A dog may thus be taught to secrete saliva half an hour after a bell is rung (*i.e.* inhibition of delay). This is known as a *trace* reflex. In the interval some definitely active inhibition must be present to prevent the stimulus from acting, since the introduction of an extraneous stimulus during the interval causes an immediate

flow. If, however, in the interval, another stimulus is applied which the dog has been taught to associate with *no* food, it is found that an inhibition of the conditioned reflex has been produced, and that the latter cannot be elicited again for some time. This we call a *conditioned inhibition*, or if the animal has had to differentiate carefully between the positive and negative stimuli, *differential inhibition*. Conditioned inhibition leads to *extinction* of the reflex,

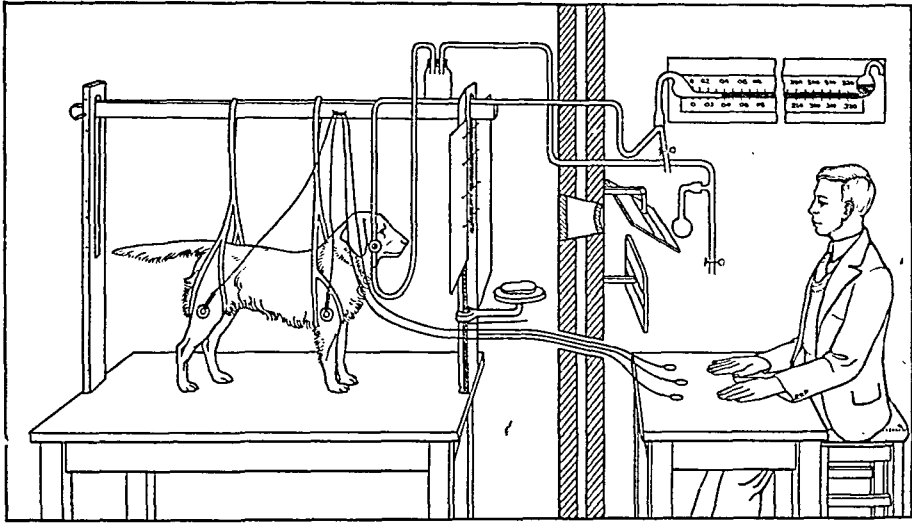


FIG. 204. (From Pavlov.)

a fact which is of considerable practical importance in relation to undesirable habits in children. When mustard is put on the fingers of a child which sucks its fingers it obtains the reverse of satisfaction from putting its fingers in its mouth and ceases to do so. All forms of inhibition other than those caused by extraneous stimuli are known as **internal inhibition**, since they involve an active inhibitory process. Evidence indicates that this inhibition occurs in the cerebral cortex. Further, it is found that if an inhibitory stimulus is repeated its after-effects may be summated, the inhibition may involve larger areas of the cerebral cortex, and other conditioned reflexes may become affected. Not only so, but the inhibition may spread more generally and the animal appears to go to **sleep**. Pavlov suggests that such sleep is closely related to hypnotic and normal sleep, which, according to this view, is due to accumulated inhibition or the receipt of stimuli which are related to cessation of activity. The observance of time of night, the ceremony of preparing for bed, provide examples of such stimuli in man. Experimental sleep is most likely to occur during differential inhibition, by repetition of thermal stimuli or

during the interval between the application of a conditioned and its associated unconditioned stimulus as in the trace reflex. The sleep produced may be very profound and during it the animal is remarkably irresponsive to stimulation. The inhibition may involve limited areas of cortex, but an inhibition produced in one analyser may spread to another adjacent, and even the motor cortex may become involved. In man also we know that sleep may be similarly patchy, and that many activities, *e.g.* walking, hearing, even reasoning, may take place during sleep.

Many attempts have been made to make diagrams of possible new paths being laid down and of short-circuits formed. Such diagrams are more fanciful than useful since the amount of exact information on such subjects is negligible. It seems indeed more probable not that new paths exist separately but that they are merely different from the old in that the impulses pass along them at too great a rate to affect consciousness. There is now evidence, however, that it is possible to establish conditioned reflexes in dogs in which the cerebrum has been removed. In these, other parts of the brain have become the analysers, but they can only appreciate comparatively crude stimuli.

Of interest appears to be the importance of *coincidence in time* in the formation of conditioned reflexes. Since a nerve impulse is self-propagating it is reasonably possible that two impulses arising at the same time in different parts of the body may eventually meet. It may be that this hitherto little appreciated point may be of fundamental importance in relation to the formation of conditioned reflexes.

Some very interesting observations in this relation have been made on animals which appear to throw light on human behaviour. For example, when an animal has acquired a positive response to an object of circular form and a negative one to an ellipse, great irritability and restlessness are observed if an object intermediate in shape is used. The state produced is comparable to that of neurasthenia in man or the irritability produced when one is unable "to make up one's mind."

It is evident that the learning of so-called tricks by the lower animals must depend on similar mechanisms. It may be that many of the problems of memory do so also, for we can readily say that the dog "remembers" the association of the conditioned with the unconditioned stimulus.

Pavlov has been able to differentiate between different kinds of nervous systems in regard to the ease with which excitatory and inhibitory states may be formed. Some are well balanced, others less so; he draws attention to similar differences which occur in human temperaments.

It is but a step from the conditioned reflexes just described to the phenomenon of acquiring **habits** or habitual actions, such as are involved in learning to ride a bicycle or drive a motor-car. The movements are, in the first instance, acquired as a result of conscious effort, but subsequently become reflex in nature and no longer involve such effort. Until we attempt to write or use a knife and fork with the unaccustomed hands we scarcely realise how many of our actions are reflex in character. In relation to posture, for example, we have a large number of inborn reflexes, but in addition to these we may by practice acquire a vast number of others, our total capability in relation to postural equilibrium being a combination of the inborn and the acquired. How far some of the still higher activities of the brain may be held to be a similar summation of inborn and acquired characteristics leads into the realm of psychology, which is outside our present province.

The Rôle of Heredity.—It is of interest to observe at this point that in spite of many experiments no evidence has been obtained that conditioned reflexes can be inherited. In these experiments the remarkable discovery was made that puppies do not appear to have any hereditary preference for meat. That is, however, not to say that the influence of heredity may not be important in determining the ease with which certain reflexes may become established. It is well recognised that it is easier to train some dogs (and some humans) than others.

The Biological Function of Conditioned Reflexes.

It is easy to develop a whole philosophy on the basis of conditioned reflexes, and to make out a case for the greater part of human behaviour being dependent on the development of such reflexes. This has been done by Pavlov and by Watson in what is known as the Behaviourist School of Psychology; its views have, rightly, not received general acceptance although they explain more than at first sight seems possible. (See McDowall, 1943.)

The importance of conditioned reflexes to the animal is that they constitute the basis of learning and give a greatly increased significance to sensations and in this way give the animal a greater appreciation of its environment. Thus it may be forewarned of danger, and the acquisition of food is also facilitated.

In civilised communities the establishment of positive and negative reflexes makes community life possible through the medium of restraints and conventions of which that of language is the most important since it makes possible the conveyance of ideas from one person to another.

CHAPTER XLVI

STRUCTURE OF THE CEREBRUM

THE cerebrum consists of two halves, called *cerebral hemispheres*, separated by a deep longitudinal fissure and connected by a large band of transverse commissural fibres known as the *corpus callosum*. The interior of each hemisphere contains a cavity of complicated shape, called the *lateral ventricles*, which are a continuation upwards of the fourth and third ventricles.

Each hemisphere is covered with grey matter (so-called because it is grey in colour when cut across) which passes down into the fissures. This surface grey matter is called the *cerebral cortex*. It varies in amount directly with the amount of convolution of the surface. Under it white matter is situated; and at the base there are masses of more grey matter. These masses consist of the *thalamus* and the *basal ganglia*, of which the most important are the *lentiform* or *lenticular nucleus* and the *caudate nucleus*, which together form the *corpus striatum*.

The Convolutions of the Cerebrum.

The surface of the brain is marked by a great number of depressions which are called *fissures* or *sulci*, and it is this folding of the surface that enables a very large amount of the precious grey matter of the cortex to be packed within the narrow compass of the cranium. In the lowest vertebrates the surface of the brain is smooth, but going higher in the animal scale the fissures make their appearance, reaching their greatest degree of complexity in the higher apes and in man. This is well seen in the figure on p. 623.

In an early embryonic stage of the human foetus the brain is also smooth, but as development progresses the sulci appear, until the climax is reached in the brain of the adult.

The following figure (fig. 205), comparing the brain of one of the lower monkeys with that of the child shortly before birth, shows the close family likeness in the two cases.

The sulci, which make their appearance first, both in the animal scale and in the development of the human foetus, are the same. They remain in the adult as the deepest and best-marked sulci; they

are called the *primary fissures* or *sulci*, and they divide the brain into *lobes*, details of which are to be found in textbooks of Anatomy. By far the most important of these is the fissure of Rolando or

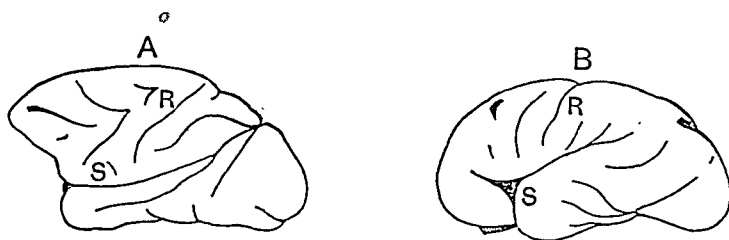


FIG. 205.

- A. Cerebral hemisphere of adult Macaque monkey.
B. Cerebral hemisphere of child shortly before birth.

The two brains are very much alike, but the growth forwards of the frontal lobes even at this early stage of development of the human brain is quite well seen. S, fissure of Sylvius; R, fissure of Rolando.

central sulcus, which is seen in fig. 206. The remaining sulci, called the *secondary fissures* or *sulci*, further subdivide each lobe into *convolutions* or *gyri*.

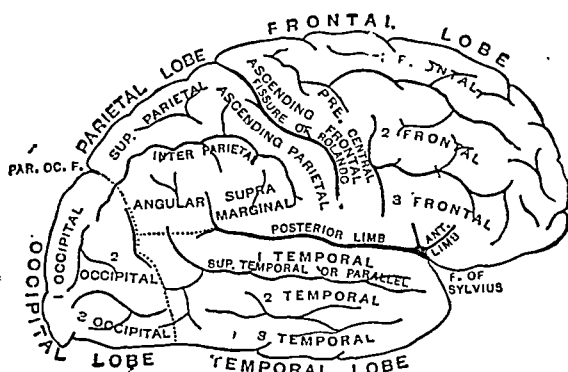


FIG. 206.—Right cerebral hemisphere, outer surface.

The White Matter of the Cerebrum.

The white matter of the cerebrum, like white matter elsewhere, is made up of medullated nerve-fibres. According to the direction of the fibres, they may be divided into three principal groups (see figs. 207 and 208):—

1. *Association fibres*.—These pass from convolution to convolution.
2. *Commissural fibres*.—These pass by the commissures of the brain, of which the most important is the corpus callosum, so as to link the convolutions of one hemisphere with the corresponding convolutions in the opposite hemisphere, where they terminate in arborisations (synapses) round the cells of the grey cortex.

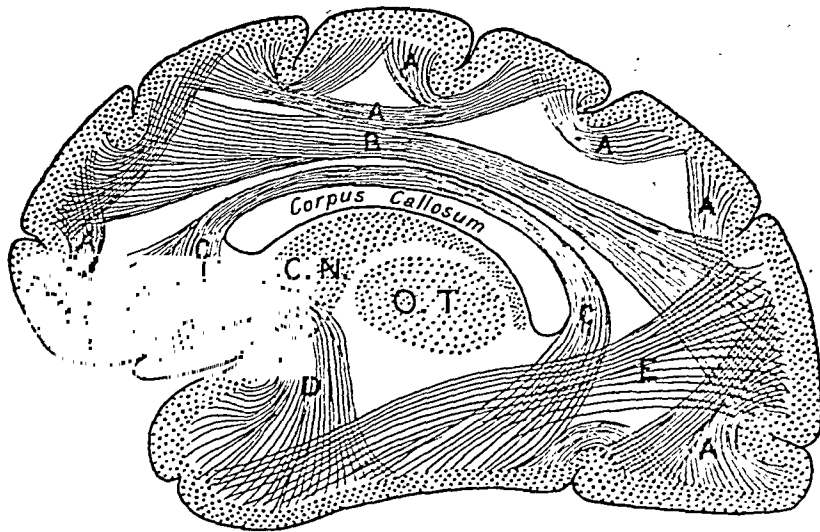


FIG. 207.—Lateral view of a human hemisphere, showing the main bundles of association fibres (Starr). A, A, between adjacent convolutions; B, between frontal and occipital areas; C, between frontal and temporal areas (cingulum); D, between frontal and temporal areas (fasciculus uncinatus); E, between occipital and temporal areas (fasciculus longitudinalis inferior); C.N., caudate nucleus; O.T., thalamus.

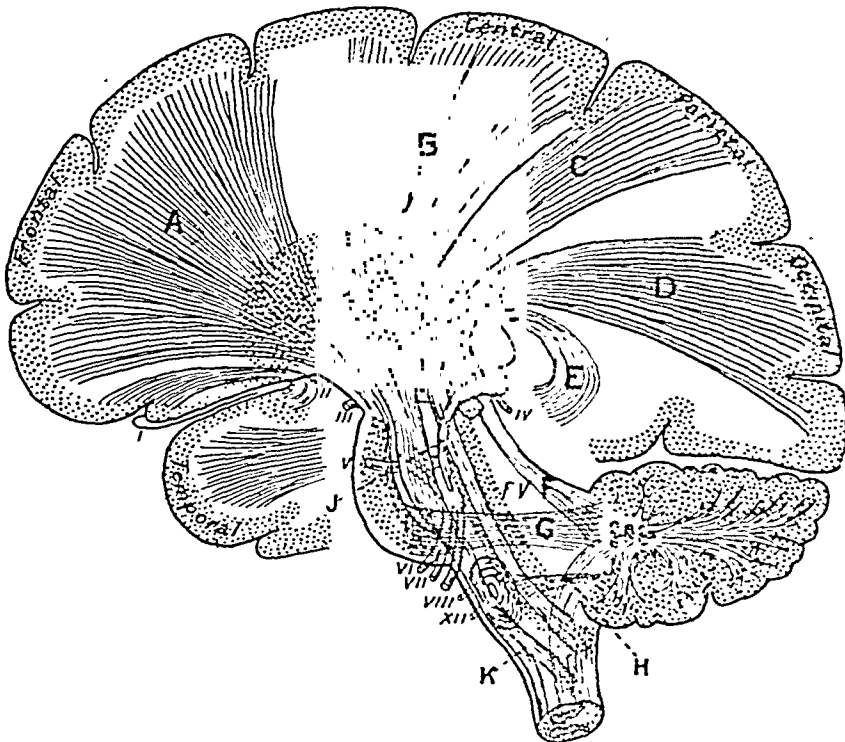


FIG. 208.—Diagram of the projection fibres within the brain (Starr). A, tract from the frontal gyri to the pons nuclei and so to the cerebellum; B, motor pyramidal tract; C, sensory tract for touch; D, visual tract or visual radiation; E, auditory tract or auditory radiation; F, G, H, superior, middle, and inferior cerebellar peduncles; J, fibres between the auditory nucleus and the inferior corpus quadrigeminum; K, motor decussation in the bulb; F, V, fourth ventricle. The numerals refer to the cerebral nerves. The sensory radiations are seen to be massed towards the occipital end of the hemisphere.

3. *Projection fibres*.—These are the fibres which run more or less vertically and link the cerebrum to the lower portions of the central nervous system. They may be divided into the efferent and afferent systems which are composed of fibres which convey impulses from and to the cortex respectively. These can best be studied from figs. 207 and 208.

Histological Structure of the Cerebral Cortex.

The cortex may be divided into six primary layers (fig. 209). These are based on the staining of cells (see Economo):—

1. *The outer fibre layer*.—This is composed of fibres derived from the dendrons of the cells of the next layer and many are afferent fibres from the white matter. The few nerve-cells intermingled with these are fusiform and branched, and have several processes which lie horizontally beneath the surface. Neuroglia cells are also present.

2. *External granular layer*.—This consists of large numbers of small cells of a variety of shapes closely packed.

3. *Pyramidal cell layer*.—This consists of medium-sized pyramidal cells, the large cells being the deepest. Branched dendrons run to the surface and laterally. The lateral processes are also branched dendrons. The axon originates from the base. This layer of small pyramids increases in depth as we ascend the animal scale; thus it is poorly developed in Insectivora, and shows an increasing degree of development in Rodentia, Ungulata and Carnivora. The maximum thickness is reached in man. Embryologically, this is the latest layer to develop, reaching its zenith after birth. The cells of this layer are believed to be association units subserving the higher mental processes. It is greatly developed in the frontal and parietal regions where the highest associations are believed to occur.

4. *The internal granular or star-pyramidal layer*.—This is like the external granular layer but is richer in fibres. This layer is a distinguishing mark of sensory areas, and is practically absent in the pre-Rolandic or motor convolutions. It is well marked in the part of the occipital cortex, concerned with sight.

5. *The ganglionic or large pyramidal layer*.—In certain regions of the cortex this contains the giant pyramids or Betz cells, which are characteristic of the motor areas. Beneath is a dense network of fibres. In the visual cortex there are a few giant stellate cells here.

6. *The inmost or fusiform layer*.—Here are many small scattered cells, many of a fusiform shape, with axons running vertically towards the surface. In the island of Reil this layer is hyper-

trophied, and is separated from the rest of the grey matter by a stratum of white fibres; it is known then as the *claustrum*. It is the first layer to appear and is almost fully developed at birth.

If, instead of the cells, the fibres are stained, *e.g.* by Weigert's method, certain lines appear as indicated in fig. 209. Sometimes

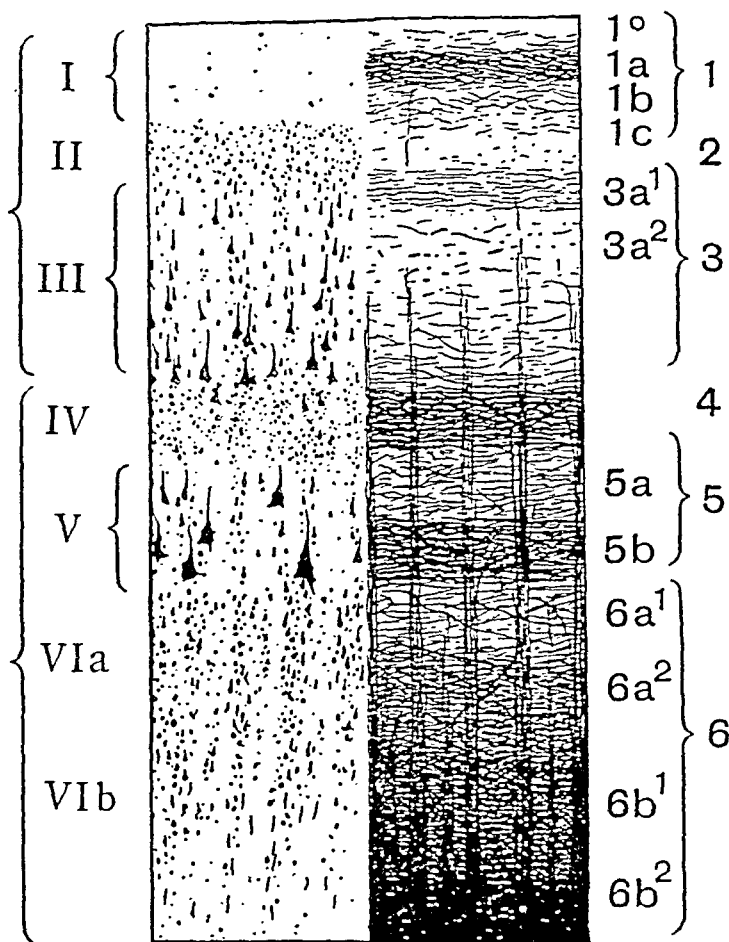


FIG 209.—Diagram of the layers of the human cerebral cortex. On the left, I—VI are the cell layers; on the right, 1—6, are the fibre layers as they appear in specimens stained by means of the Weigert-Pal method. Layers 4 and 5 (b) are respectively the external and internal lines of Baillarger. (Economo.)

as in the occipital cortex a white line may be seen with the naked eye (Gennari), like a white thread in the grey matter.

Detailed examination shows that the line may be divided into light and dark bands (Baillarger) which vary very much in different parts of the cortex. In such sections groups of vertical fibres running out to the second layer are also seen.

The functions of the cell layers.—It is important to note that the cells of the cortex are arranged in vertical chains and that each layer is attached to those without and within it. It seems most probable that eventually various patterns of cell and fibre network will eventually be made out and related to the activity of each part. Also it has been seen that certain layers are specially developed in certain regions: This and their order of development in certain animals and in mental defectives has led to conclusions regarding the function of the layers.

The inner layer may be regarded as the fundamental cell layer, the others being formed from it from within outwards, in both embryonic and historical development.

The inner cell layers are probably concerned with the performance of organic and instinctive activities, and there is but little difference seen here between man, monkey, and dog. The middle pyramidal layers are considered to be concerned with the reception and transformation of afferent impulses. The outer layers, on the other hand, are concerned with the intellectual or associational functions. Defect of development of the outer layers leads to various forms of *amentia* (inborn lack of mental development, or idiocy); in *dementia* (degenerative mental change coming on later in life) there are retrograde changes in the upper layers of cells.

In the hippocampal region the cortex is simpler in structure than elsewhere. It consists essentially of three layers only:—(1) Molecular layer; (2) external pyramidal layer; (3) inmost or fusiform layer. Of these 1 and 2 are unusually thick. This part of the cortex is concerned with the sense of smell, which is a primitive sense, and is therefore subserved by a primitive type of cortex representing the archipallium or primitive brain.

Embryology of the Cerebrum in relation to Function.

Flechsig's embryological method has given us valuable knowledge of the structure and functions of the human brain. The method depends on the fact that various tracts of fibres become myelinated, *i.e.*, acquire their medullary sheath at successive periods of time in development. The myelin sheath appears three or four months after the axis cylinder is formed. The Weigert method of staining renders the detection of a medullary sheath an easy task. Flechsig's method is in short the complement of the Wallerian method. In the former method the tracts are isolated by differences in the time of development of the myelin sheath; in the latter method, the same object is obtained by observing the degeneration which is most noticeable in the same sheath.

In the central nervous system the afferent projection fibres are myelinated first; the efferent projection fibres and the association fibres are myelinated later. Thus in the human foetus the peripheral nerves and nerve-roots become myelinated in the fifth month of intra-uterine life; of the tracts in the cord, those of Burdach and Goll (*exogenous* fibres springing from the cells of the spinal ganglia) are the first to be myelinated; next come the tracts of Flechsig (dorsal cerebellar) and of Gowers (ventral cerebellar): these are *endogenous* fibres springing from cells within the cord. All these tracts are afferent. The pyramidal tracts, the great efferent or motor

channels, are not myelinated until after birth. The whole afferent tract is myelinated at birth; these fibres are *in utero* exercised in conveying impressions to the afferent reception centres, the stimuli arising from contact of the foetal integuments with the maternal tissues. There is also early myelination round the calcarine fissure in the visual sphere, and in connection with the areas related to other special senses; this is shown in fig. 210.

Ambronn and Held confirmed Flechsig in finding that the afferent fibres are myelinated before the efferent, in the central nervous system, but in the nerve-roots this is reversed, the anterior root-fibres being myelinated before the posterior.

Held also demonstrated the important influence of stimulus on myelination. His experiments were made on cats, dogs, and rabbits, which are born blind. If light is admitted to one eye by opening the lid, more obvious myelination is subsequently found in the corresponding optic nerve than in that of the opposite side.

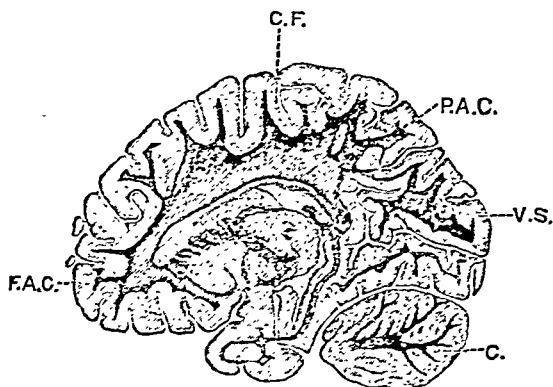


FIG. 210.—Diagram of vertical section of the brain of a child 5 months of age. The greater part of the white matter now shows myelination, thus indicating development of the association centres. (After Flechsig; Weigert method of staining.)

This is not due to the irritation caused by forcibly opening the lid, for if the lid is opened and the animal kept in the dark, no difference in the myelination of the two optic nerves is observable. Flechsig also showed that a child born at eight months had more marked myelination of its optic nerves, a month later, than a child born in the usual way at the ninth month.

The richness of the brain in myelinated fibres increases for many years after birth with the progress of intellectual development. Kaes states this continues up to forty years of age, and that in old age the number diminishes. Myelin appears to be necessary for the functional activity of nerve tracts, and its development progresses *pari passu* with development of function; the reverse change (atrophy and degeneration) correspondingly accompanies marked disturbances of function.

Flechsig's Myelogenetic Cortical Fields.

In the cerebral convolutions the fibres become myelinated in a strictly regular sequence; some convolutions have their fibres medullated three months before birth, while in others complete myelination has not occurred six months later. Fibres of equally great importance become medullated at the same time; those of primary importance first, and so on. In this way, cortical fields can be mapped out, thirty-six in number. Flechsig divided them chronologically into three groups, *primary*, *intermediate*, and *terminal*. The primary fields, the seats of sensory representation, are most darkly shaded in figs. 211 and 212. These are also connected with outgoing tracts. The terminal areas (unshaded) are not myelinated until at least a month after birth. These and the majority of

the intermediate areas show few or no projection fibres even eight months after birth. They comprise, in fact, the association centres, and are rich in long association fibres. Subsequent work by Brodmann on a cytohistological basis has indicated that there may be as many as 160 different areas.

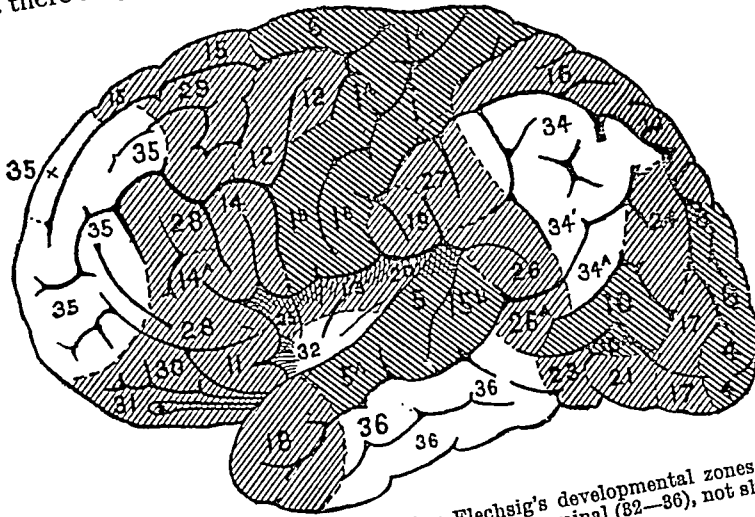


FIG. 211.—Outer surface of human brain, showing Flechsig's developmental zones; primary (1—10) darkly shaded; intermediate (11—31), less deeply shaded; terminal (32—36), not shaded. (Flechsig.)

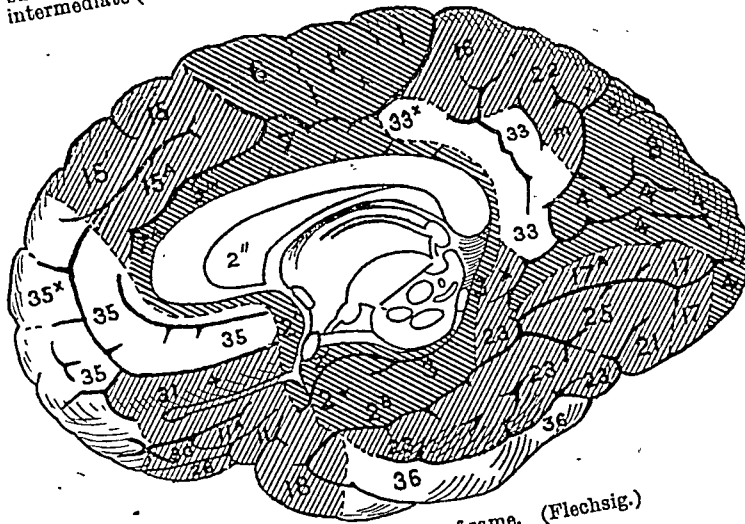


FIG. 212.—Inner surface of same. (Flechsig.)

FUNCTIONS OF THE CEREBRUM

The cerebrum is the seat of those psychological or mental processes which are called volition and feeling; volition is the starting-point in motor activity; feeling or consciousness is the final phase of sensory impressions; the correlation of sensations with one another, and with volitional impulses so generated, constitutes thought. That

the brain is the organ (or anatomical correlate) of mind is to-day a matter of such common knowledge that it is almost superfluous to mention it in a physiological text-book. Yet its functions were entirely unknown or only dimly conjectured by ancient philosophers, and the overwhelming importance of the grey matter on its surface in mental phenomena is a discovery of comparatively recent date.

The functions of any organ may be discovered by a variety of procedures, each of which has been applied to the cerebrum as a whole and to its parts.

(1) The relative **development** of the organ according to position in the animal scale (p. 625).

(2) The **histological structure**. A study of the cell layers suggests the relative importance of the various parts of the brain. These have already been discussed (p. 617).

(3) **Extirpation** or removal of the whole or part of the organ.

(4) **Stimulation** of the cortex in various ways may cause **movements** and stimulation of sense organs and may set up **action potentials** in the cortex.

(5) **Diseases** of the organ may be studied. In the case of the cerebrum these correspond either to extirpation or to stimulation.

(6) The **establishment of conditioned reflexes** (see p. 627) prior to localised removal. (Fulton, Hines, Economo)

Effects of Complete Removal of the Cerebrum.

The brainless frog which we have studied in relation to the functions of the spinal cord is also a useful object-lesson to teach us the uses of the part removed, by observing in what manner the animal differs from one which has its brain intact. If, instead of taking a frog, we take an animal lower in the scale, where the brain is not so fully developed, the effect of removing that organ will be less marked; whereas if we remove the brain in a more highly developed animal, the simultaneous removal of the brain functions will be naturally more noticeable. We have already seen that the development of the cerebral hemispheres increases in importance as we rise in the animal scale.

If the cerebral hemispheres are removed in a teleostean or bony fish (and in such animals there is only a rudimentary cortex), the animal is to all intents and purposes unaffected; it can distinguish between a worm and a piece of string, and will rise to red wafers in preference to those of another colour. The operation does not damage the primary centres of vision (the optic lobes, which correspond to the corpora quadrigemina of the mammal), and in these fishes the eye is the most important sense-organ.

A shark, however, subjected to the same operation, is reduced to a condition of complete quiescence; this is due to the circumstance that in this fish the principal sense-organ is that of smell, and severance of both olfactory tracts produces the same result as removal of the entire cerebrum. In either case the path between the olfactory bulbs and the centres that control the cord are interrupted.

In the frog we find that removal of the hemispheres only does not entirely abolish its apparent spontaneity; it still continues to feed itself, for instance, by catching passing insects. It is not until the thalami are removed also that it becomes a purely reflex animal. If the brain and the anterior end of the bulb are removed the lower

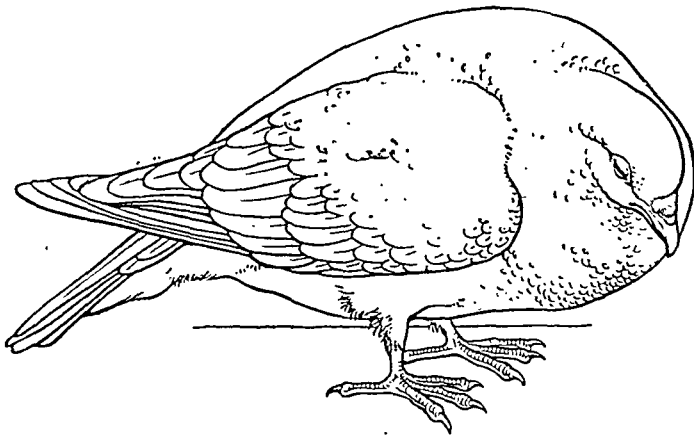


FIG. 213.—Pigeon after removal of the hemispheres. (Dalton.)

centres of the cord are set free, and the result is incessant movement provoked by slight stimuli.

A bird from which the cerebrum has been removed remains perfectly motionless, sleepy, and unconscious (see fig. 213) unless it is disturbed. When disturbed in any way it will move; for instance, when thrown into the air it will fly. But these movements are, as in the frog, purely reflex in character; when the animal is made to fly its movements are directed by visual stimuli, the visual apparatus being still intact, and it will select a perch to settle on in preference to the floor. It will start at a noise; it will not eat voluntarily; it exhibits no emotions such as fear, sexual feeling, or maternal instincts.

In mammals the operation of extirpation of the brain is attended by such severe hæmorrhage that the animals die very rapidly, but in some few cases where they have been kept alive, the phenomena they exhibit are similar to those shown by a frog or pigeon. The difficulty of the operation was overcome in dogs by Goltz of Strasbourg, who removed the cerebrum piecemeal. One dog

treated in this way lived in good health for eighteen months, when it was killed in order that a thorough examination of the brain might be made. It was then found that not only the cortex but the main parts of the thalamus and corpus striatum had been removed also. Though it could still carry out co-ordinated movements, its reactions were entirely reflex, and memory, emotions, and the capacity to learn were absent.

The results of the operation become progressively greater as we ascend the scale. The higher the animal, the more fatal the effects, the more severe the immediate disturbance, the slower the return of function, and the greater the permanent loss.

This is anatomically explicable when we remember that in the lower animals the pyramidal pathway is insignificant, and when it is interrupted the disturbance is consequently slight. In animals below the mammals it is absent, and going up the mammalian scale it becomes more and more important, as the following figures show:—

In the mouse the pyramidal fibres constitute 1·14 per cent. of those in the cord:					
„ guinea-pig	„	„	3·0	„	„
„ rabbit	„	„	5·3	„	„
„ cat	„	„	7·76	„	„
„ man	„	„	11·87	„	„

We can therefore quite readily understand that in the apes and in man, a damage to the cortex which causes degeneration of these tracts will cut off many impulses to the anterior cornual cells, and produce a considerable degree of paralysis.

The Effect of Removal of the Cerebral Cortex.

This is characterised by a loss of all reactions which the animal has learned in its lifetime. There also occurs a remarkable state of sham rage (Bard). This is due to a release of hypothalamic activity, for removal of the hypothalamus produces a cessation of symptoms, while it is produced by stimulation of the hypothalamic region.

Decerebrate Rigidity has already been dealt with on p. 599. It is not produced by removal of the cerebellum alone but only if part of the red nucleus is removed also.

Localisation of Cerebral Functions.

The different parts of the brain and of its cortex are related to different parts of the body. The right hemisphere, for instance, controls the voluntary movements on the left side of the body, and receives sensory impulses from the left side, and *vice versa*.

In each hemisphere there are certain areas, termed *motor areas*,

which are the starting-points of those volitional impulses which give rise to movements; and other areas primarily concerned in the reception of sensory impulses; these are termed *sensory areas*. These various areas have been mapped out by means of experiments on animals, and by the observation of disease in man.

It must, however, be understood that the idea of those centres is merely a convenient convention. The areas or centres are but recognisable points in a very complicated system of reactions. The brain really acts as a whole. Let us take an example, and imagine the smell of an orange; such an abstract idea of an isolated sensation is impossible; we cannot think of the smell of the orange apart from the other characteristics of the fruit, the smell recalls the taste, the shape, the colour, the act of peeling it, fingering it, cutting it, eating it, and so forth. One sensation due to the activity of one area, such as the olfactory area, calls into play the activity of other sensory areas, and of the motor areas, and of the links between the sensory and motor areas. The brain is acting as a whole because its various parts are called into play simultaneously, though the whole brain is not concerned in each of the component sensations and volitions associated with any particular mental state.

Moreover, the doctrine of cerebral localisation is not accurately expressed by the statement that a cortical centre is one, the stimulation of which produces a definite response, and the extirpation of which abolishes the response. We shall, for instance, see below that the stimulation of certain areas in the dog's brain produces certain movements, but Goltz showed that in his dogs the removal of an entire hemisphere did not cause permanent paralysis of the opposite side of the body, nor does it do so in children.

In the central nervous system there are few or no places where only one set of nerve units is situated, with fibres passing to or from them. Every locality has several connections with other parts, and also fibres passing through it which connect together the parts on all sides of it. Hence in extirpating even a limited area, numerous pathways are interrupted, and the damage is consequently widespread. Much of the disturbance produced at first gradually passes away, and the *temporary* effects must be distinguished from those which are *permanent*; the permanent effects have the greater significance of the two. Moreover, it is clear that the relative and absolute value of any locality in the central nervous system depends largely on the degree to which centralisation has progressed, and on the amount of connection between the various areas. The closer the connection, the more numerous and intricate the pathways, the greater will be the permanent effects of an extirpation, and the recovery of function the more remote. The lower the

animal in the zoological series, or the less the age of the animal, the more imperfectly developed will be the connecting strands, and so the possibility of other parts taking up to some extent the functions of those that are removed will be increased.

Modern researches have brought out the overwhelming importance of the cortex; it contains the highest cerebral centres.

The Motor Area.—The first work was carried out by Fritsch and Hitzig on dogs. They found that the motor area was situated in the neighbourhood of the crucial sulcus, which probably corresponds to the fissure of Rolando in man.

The most important experiments on this subject were those of Sherrington and Leyton, who made a number of experiments on monkeys, and the human brain so far as it has been examined has given similar results.

The elucidation of this area has been most successfully carried out by **stimulation** by the method of Sherrington. The brain in an anæsthetised animal is exposed and stimulated with a weak faradic current, one electrode being placed on the brain, and the other attached to an indifferent part of the animal's body. This allows of finer localisation than is possible with the ordinary double-point electrodes.

By such means it has been found that stimulation of the part of the ascending frontal convolution, which lies immediately in front of the fissure of Rolando (central sulcus), causes movement of the opposite side of the body. Small groups of muscles may be caused to contract and from no other region can such movements be so easily elicited.

This motor area (area 4) has now been shown to be much narrower than originally described as it extends into the fissure. Older descriptions included the premotor area 6a (see fig. 214).

The proof that the properties of the motor area depend on its pyramidal cells is based on three pieces of evidence. Stimulation of the area is ineffective before the cells have developed in infant *Macacus* monkeys, after it has been coagulated by heat (Barenne) or after section of the pyramidal tracts (Marshall and Towers.) As we shall see later, these **pyramidal tracts** are the main pathways by which the impulses responsible for voluntary movement travel.

It cannot fail to strike even a superficial observer how large the cortical area is which deals with movements of the head and arm regions when compared with that of the lower limb, and still more with that of the trunk. The trunk itself has a larger mass of muscular tissue, but it is in the head region (which includes the complex movements of the tongue and such structures as the vocal cords) and in the arm and hand that the movements are most varied

and most delicate. No doubt this is the explanation of the greater size of their cortical representation.

The excitability of this region depends on the integrity of the underlying pyramidal cells and disappears if they are destroyed. Cyclic spontaneous fluctuations of excitability occur and are reduced after stimulation. It is extremely sensitive to acid-base changes. Increased acidity causes the excitability and alkalinity the cyclic changes to disappear.

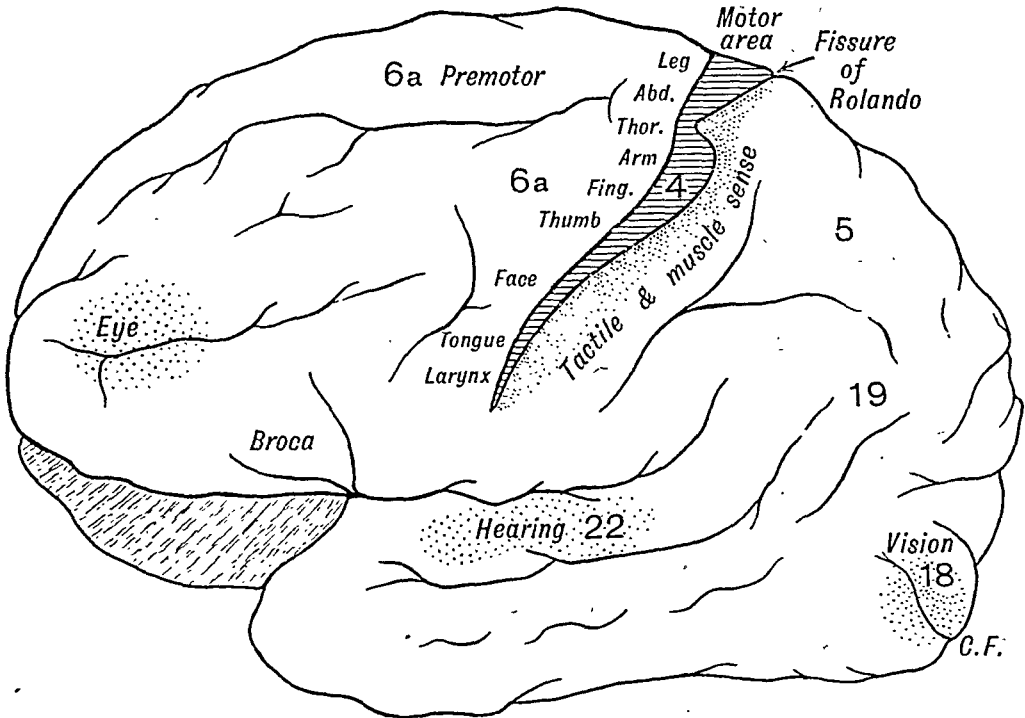


FIG. 214.—Brain of man. Left hemisphere viewed from side and above so as to obtain the configuration of the Rolandic area. The figure involves some foreshortening about both ends of the sulcus centralis or fissure of Rolando. The extent of the so-called motor area on the free surface of the hemisphere is indicated by black stippling which extends back to the central sulcus. Much of the "motor" area is hidden in sulci: for instance, it extends into the central sulcus. (After Brodmann and Vogt.)

Premotor Area.—Close to the motor area proper are less excitable areas, stimulation of which gives less discrete movements (areas 3 and 6), but these movements are abolished by removal of the motor area. This area is less excitable, requiring a rate of 4 per second compared with 7 to 20 for area 4. The area has no Betz cells (Fulton).

There is great variability in the excitability of this part of the cortex from time to time and the muscles which contract may be varied by stimulation of the sensory part of the cortex, and it has been found that as one set of muscles contracts there is reciprocal relaxation of another (see Reciprocal Innervation).

If the stimulation used is too powerful the movement spreads to other parts, and a considerable portion of the body may be thrown into convulsive movements similar to those seen in epilepsy.

Other Motor Areas.—In addition to the movement of limbs and trunk, it is possible from the regions indicated in fig. 214, to obtain conjugate movements of the eyes with constriction of the pupil, movements of the larynx and of the muscles of respiration. A motor area for the eyes is also present in the inner aspect of the occipital lobes.

Extirpation or removal of the motor area produces paralysis of the same groups of muscles as are thrown into action by stimulation. It also leads to degeneration of the whole pyramidal tract which arises from this region.

In monkeys there is some recovery especially of proximal joint movement, but the finer patterns of response are not regained. A similar recovery may occur in man, but practically none in the hand. Almost complete recovery has been described after complete loss of the motor area in children.

The reflexes are depressed but later become exaggerated. A flaccidity of muscles generally persists. In this latter point ablation differs from pyramidal tract lesions, in which characteristic rigidities appear. Extirpation of the frontal lobe does not, however, affect the conjugate movements of the eyes in man.

Removal of the motor cortex causes no sensory loss but there may be vasomotor changes and shivering.

The study of **injury** or **disease** indicates that the effect of either removal or stimulation may be produced. An example of the former is seen in the effect of a hæmorrhage on the surface of the brain such as occurs sometimes at birth. It results in a degeneration of that part of the pyramidal tract which is composed of fibres from the portion of the cortex injured, and a corresponding region, commonly a limb on the opposite side of the body, is paralysed (see also Voluntary Movement).

On the other hand, a tumour or a spicule of bone after an injury may irritate the motor area and set up movements of one particular part of the body (*Jacksonian epilepsy*), which may spread and cause general convulsive seizures. The cause of irritation is often removed surgically, and if the surgeon is in doubt as to the exact region irritated, he may stimulate the suspected part to find if it produces the same movements. No more striking proof of the value of purely scientific animal experiment exists than the cure in an individual of Jacksonian epilepsy, and such brain surgery emphasises the necessity for knowing the surface marking of the various areas.

Some parts which normally move together are innervated from

both sides of the brain, *e.g.* the upper part of the face, and are not entirely paralysed by unilateral lesions.

Removal of the premotor area (6a) leads to characteristic disturbance of posture including an exaggeration of the grasp reflex of the fore-limb. There is only a disturbance of skilled movements. The spasticity affects particularly the antigravity muscles due to release of the extrapyramidal system (Fulton). It is believed that from this region the extrapyramidal system begins and that impulses pass from it to the basal ganglia (Fulton).

The Motor Areas and the Autonomic System.—A large number of changes such as vasoconstriction, vasodilatation, cardiac acceleration and slowing, and gastro-intestinal changes can be produced by stimulation of areas 4 and 6 (Fulton).

The Sensory Areas.

The Sensory Areas.—The methods used in the study of the sensory cortex have necessarily been less direct than in the case of the motor cortex but in general have been similar. In many cases careful anatomical dissection has pointed the way. The study of this subject was initiated by Ferrier at King's College, London.

Stimulation.—In animals, it is difficult to say when a sensation is experienced, but this may be assumed from the indirect evidence in the form of reflex movements which usually accompany sensation; thus on stimulating the *auditory area* there is a pricking up of the ears; on stimulating the *visual area* there is a turning of the head and eyes in the direction of the supposed visual impulse. That such movements are reflex and not direct is shown by the long period of delay intervening between the stimulation and the movement. Some experiments have, however, been made on man (see below).

Barenne has found that chemical stimulation of a sensory area by strychnine may cause symptoms of local pain, *e.g.* a limp on the part of the animal or hyperæsthesia of the part concerned.

Extirpation of a sensory area leads to loss of the sensation subserved. Since a study of sensation in animals is so difficult the majority of the observations have to be made on man after **injury** or **disease**. In Jacksonian epilepsy, due to localised irritation of the cortex, *e.g.* by a spicule of bone after a cranial injury, the convulsions may be preceded by a sensory aura, or indefinite sensation corresponding to the region irritated.

Extirpation has also been used in combination with **conditioned reflexes** on trained animals. The animals lose those responses which depend on the areas removed.

The **action potentials** of the various regions of the cortex in response to peripheral stimulation have also been used to trace

pathways and have shown that animals vary very much in the amount of sensory representation which a part of the body, such as the foot or snout, may have on the cortex. (Adrian.)

The Parietal Area.—Stimulation of the post-central gyrus immediately behind the fissure of Rolando (central sulcus) produces no direct movements; and extirpation leads to no motor paralysis, and no degeneration of the pyramidal tracts. Histological examination of the parietal grey matter shows it, moreover, to possess the structure of a sensory rather than of a motor area.

Anatomical studies had shown that there existed a fan-like projection system of fibres between the thalamus and the parietal cortex and each of the methods referred to have indicated that sensory impulses are transmitted to the post-central gyrus and to the posterior lip of the precentral gyrus. Moreover, it has been found that the sensory area for the arm is in the same level as the corresponding motor area (Penfield and Boldrey).

Experiments of strychninisation of the cortex, of ablation in trained animals, and a study of the electrical responses to peripheral stimulation have been confirmed by direct experiments on man. Patients whose cortices have been exposed for other reasons have permitted electrical stimulation of the region. The sensations experienced have not usually been very definite, *e.g.* those of constriction, numbness and tingling (Cushing). Pain is unusual but has been described as arising from areas 5 and 7 by Foerster. The sensations are referred to definite peripheral parts such as the arm or leg.

The experiments of Dusser de Barenne at Yale indicate, however, that the sensory representative in the cortex is not like the motor area confined to a narrow strip, but that from the face, arm, and leg extends backwards across the whole parietal region. It has not, however, been found that strychninisation produces any hyperæsthesia of the body.

Loss of the parietal region in man and monkeys leads to results which the foregoing would suggest. There is a loss of the power to differentiate between weights and shapes. Some late improvement occurs but more in the trained chimpanzee than in man (Ruch, Fulton and German). Sometimes a patient loses his sense of awareness of the existence of a part of the body (apart from sight). This leads to a virtual paralysis, for the subject cannot use the limb properly, as when the posterior roots are cut in an animal the limb is not used.

Commonly, there are marked psychological changes and disturbances of speech (see Speech).

The parietal lobe generally is the part of the brain which shows the highest development histologically. Just posterior to the

sensory region is a large association area wherein we believe ideas regarding multiple sensations are associated. If this region is destroyed the patient loses the power of recognising objects by touch (astereognosis).

The Visual Area 18.—The lower the animal in the series, the more readily can its actions be controlled by sensory impulses which have not passed through the cerebral cortex. A decerebrated bony fish can distinguish colours, a frog can catch flies, even a pigeon will select its perch, though it takes no notice of food or of people who try to frighten it. A dog similarly operated on is practically blind, though it will blink at a bright flash of light. In the lower animals the impulses pass in to the primary visual centre in the optic lobes which acts as the centre for the reflex; as we ascend the animal scale, the path *via* the cortex becomes more permeable, of greater value, or even indispensable, and the reflexes through the lower centres are of less importance; not only so, but there are subdivisions of the visual cortical area, which correspond to different regions of the retinae.

We may in fact speak of the visuo-sensory field in the cortex as the *cortical retina* upon which the impulses from the actual retina in the eye are projected, in a manner analogous to the way in which the field of vision is projected upon the actual retina.

In the fishes which have no cerebral cortex, the optic lobes, analogous to the C. quadrigemina, are the centres for vision. In some fishes, a small number of the fibres of the optic nerves pass into the geniculate body, which forms a cell-station on the road to the posterior region of the cerebrum, where a primitive cortex begins to appear. On ascending the animal scale, this group of fibres becomes more and more abundant, and this part of the cortex becomes more elaborate in structure. When we reach the monkeys, this part of the brain is cut off from the rest by the parieto-occipital fissure to form a distinct occipital lobe. This fissure is called the *ape's split*. In the lower monkeys this lobe is quite smooth, but as the great parietal association centres get larger with increase of intelligence, the visuo-sensory area is pushed back, and the lobe thrown into folds. In the highest apes, and in the lower races of mankind, a good deal of the visuo-sensory sphere is still seen on the external cerebral surface; but in the higher races, most is pushed round on to the mesial surface.

- Some animals have *panoramic* and others *stereoscopic* vision.* The former (mainly vegetable feeders) have eyes set laterally; each eye receives a different picture, and the decussation of the optic nerves is complete; each eye sends impulses to the opposite hemi-

* According to Elliot Smith the development of stereoscopic vision has been an important cause of the advancement of the higher mammals.

sphere. Animals with stereoscopic vision have the eyes, as in man, in front, and the optic axes can be converged so that an object is focused with both eyes. This becomes necessary in carnivora, which have to catch moving prey; the more complex the movements of the fore-limbs, the greater becomes the necessity for fixation of the eyes to guide them. In such animals each visual area corresponds to the same half of both retinae, that is, to the opposite half of the visual field; the lower half of each area corresponds to the upper half of each half field of vision, and *vice versa*. The appearance of the macula lutea in the primates is the culminating point in visual development among the mammals (Holmes and Lister). Macular representation is, however, bilateral and at the tip of the occipital lobe.

A man or animal which loses both eyes is blind, but in time manages to find its way about. This is not the case when blindness is produced by removal or disease of both occipital lobes; here, the sense of orientation is lost also, for the association of sensory memories and motor impulses is then impossible.

Removal of one occipital lobe will be followed by different results in the two classes of animals just referred to. In those with panoramic vision, the result will be blindness of the opposite eye, because the decussation of the optic nerve is complete at the chiasma. But in animals such as monkeys with stereoscopic vision (in which the only decussating fibres are those which come from the inner halves of the two retinae) removal of one occipital lobe, or disease of that lobe in man, produces blindness of the same side of each retina, or inability to see the opposite half of the visual field. This is called *hemianopsia*; the head and eyes are turned to one side, namely, the side of injury (*conjugate deviation* to the side of the injury). Such an operation does not destroy vision in the central portion (*macula lutea*) of either retina, because each macula sends impulses to both sides of the brain. Stimulation of one visual area leads to a subjective sensation apparently coming from the same halves of both retinae, and also excites the solitary cells of Meynert; this produces *conjugate deviation of head and eyes* towards the opposite side to that stimulated.

These solitary cells are so called because they are few and far between; they are large cells not at all unlike the Betz cells of the motor cortex. Their axons, no doubt, pass in long association tracts to the motor eye centre of the frontal region and to the corpora quadrigemina.

The optic radiations consist of (1) sensory fibres from the optic tracts *via* the external geniculate bodies and in the lower animals *via* the pulvinar of the thalamus; (2) efferent fibres to the centres

for eye-movements; and (3) association fibres, which are last developed. The last-named link one convolution to others, and the two hemispheres together, and bring about association of ideas of vision in both hemispheres, and with other sensations. A large collection of such fibres runs horizontally through the grey matter. This white stripe is often visible to the naked eye; it is the anatomical mark of the *visuo-sensory cortex*, and is called the *line of Gennari*. The *visuo-psychic* region which adjoins the visuo-sensory area has no line of Gennari, but possesses many small and medium-sized pyramidal cells in its outer layers, which play the part of association units, where memory pictures are stored and visual sensations correlated with those from other sense-organs; the higher one ascends the animal scale, the greater becomes the depth of this layer. (See also Vision.)

The Auditory Area 22.—It has now been shown that the upper temporal convolution is concerned with the perception of hearing though it is by no means easy to ascertain whether or not an animal is deaf, but Pavlov's method of producing conditioned reflexes has now furnished a test. It is doubtless surrounded, as are the visuo-sensory area and other sense areas, by a psychic or association sphere, and is connected to surrounding parts, and especially to the visual area, by annectent gyri. Much of the auditory area is situated in the depth of the posterior limb of the Sylvian fissure where the gyri transversales which cross it are found. Destruction of both temporal lobes does not cause complete deafness but the disturbance of hearing is considerable and affects both acuity and auditory localisation. Abnormal sounds may be heard, *e.g.* buzzing.

In lesions of the left side in right-handed persons there are commonly disturbances also of speech, especially of the appreciation of speech, such as recognition of the names of objects. Sometimes auditory manifestation may usher in an epileptic fit or a "dreamy state" (Hughlings Jackson). In abscess of the temporal lobe there may be loss of vision from injury to the optic radiation. Stimulation of the auditory area in conscious subjects arouses sensations of buzzing, roaring and giddiness. (See also Hearing.)

Taste and Smell are closely connected; their cerebral area is the uncinate and hippocampal gyrus, and the tip of the temporal lobe. These parts are relatively more important in animals which rely upon smell and the oral sense for their guidance. This part of the cortex is of simpler structure than the rest, and on account of its early appearance in the animal scale is known as the archipallium or primitive brain.

The Silent Areas.—On referring once more to the maps of the brain, it will be seen that there are many blanks; one of these is in the anterior part of the frontal region. Extirpation

or stimulation of this part of the brain in animals produces but little result. The large size of this portion of the brain is very distinctive of the human brain, and it has therefore been supposed that here is the seat of the higher intellectual faculties. Such a question is obviously very difficult to answer by experiments on animals. A study of the symptoms of **tumour of the frontal lobe** indicates that this part of the brain plays a considerable part in the intellectual functions. There are commonly described, as a result of such tumours, loss of mental acuity, stupid mistakes, loss of memory and of the power to supervise; frequently, however, the patient is certified insane, before the tumour is diagnosed. The celebrated American crowbar accident is frequently quoted in this relation; owing to the premature explosion of a charge of dynamite in one of the American mines a crowbar was sent through the frontal region of the foreman's head, removing the anterior part of his brain. Although fit physically when he returned to work, he was practically useless mentally, having lost just those higher functions which are so important in the superintendence of other people. It has been found also in monkeys that although removal of this part of the brain did not interfere with the recently acquired responses to simple stimuli it did interfere with responses which required any material memory on the part of the animal. Fulton describes the occurrence of a "rather fatuous equanimity of spirit" which one encounters in a good-natured drunkard but never in a normal chimpanzee. These changes, however, occur in monkeys only after bilateral extirpation. In man the sense of well-being which may result from the removal of a tumour of the frontal lobe or of merely cutting the thalamo-frontal fibres is recognised as characteristic, and the latter operation is practised for the treatment of severe mental depression. There is, however, some tendency for the occurrence in adults of a somewhat juvenile mentality. Mott's observations on lunatics show that this region is important for intellectual operations, though not so important as the **parietal association area** behind the Rolandic area; the greater the intellectual development, the larger and more convoluted does this parietal region become.

The association fibres have been the subject of special study by Flechsig, who has shown that in the development of the brain these are the last to become myelinated; white fibres do not become fully functional until they receive their medullary sheath. This coincides with the well-known fact that association of ideas is the last phase in the psychical development of the child. It has been shown that the frontal convolutions are connected by important association tracts with the more posterior regions of the brain (see fig. 207, p. 624), and there is therefore

no difficulty in understanding that the frontal convolutions play the part of a centre for the association of ideas or, in other words, for intellectual operations.

There is some evidence that in right-handed persons the left frontal lobe is more essential for consciousness than the right, since ligature of the arterial supply of the latter has a much greater effect on apparent consciousness than ligature of the right side. (Fulton, Hines.)

CHAPTER XLVII

SENSORY NERVE-ENDINGS

ALTHOUGH different types are described, it must be understood that many intermediate forms occur.

Pacinian Corpuscles.—These are named after their discoverer Pacini. They are little oval bodies, situated on some of the cerebro-spinal and sympathetic nerves, especially the cutaneous nerves of the hands and feet, where they lie deeply placed in the true skin. They occur on the nerves of the mesentery of some animals such as the cat. They have been observed also in the pancreas, lymphatic glands, and thyroid glands, as well as in the penis. They also are present in the fascia of muscle, etc., where they probably originate the pains of fibrositis, a common variety of “rheumatism.” They are about $\frac{1}{12}$ inch long. Each corpuscle is attached by a narrow pedicle to the nerve on which it is situated, and is formed of several concentric sheaths of connective tissue, each layer being lined by endothelium (fig. 216); through its pedicle one or more nerve-fibres pass; these lose their medullary sheaths and enter a central core, at or near the distal end of which they terminate in an arborisation. Some of the layers are continuous with those of the perineurium, but some are super-added.

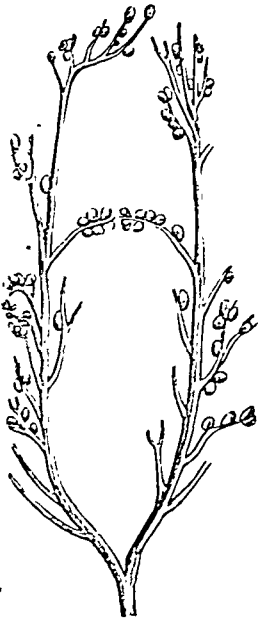


FIG. 215.—Extremities of a nerve of the finger with Pacinian corpuscles attached, about the natural size. (Adapted from Henle and Kölliker.)

End-bulbs are found in the conjunctiva (where in man they are spheroidal, but in most animals oblong), in the glans penis and clitoris, in the skin of the lips, in the epineurium of nerve-trunks, and in tendon; each is about $\frac{1}{800}$ inch in diameter, oval or spheroidal, and is composed of a medullated nerve-fibre, which terminates among cells of various shapes (fig. 218).

Touch-corpuscles (Meissner's corpuscles) (figs. 217, 219) are

found in the papillæ of the skin of the fingers and toes. They are oblong, about $\frac{1}{250}$ inch long, and $\frac{1}{800}$ inch broad; each is composed



FIG. 216.—Pacinian corpuscle of the cat's mesentery. The stalk consists of a nerve-fibre (N) with its thick outer sheath. The peripheral capsules of the Pacinian corpuscle are continuous with the outer sheath of the stalk. A blood-vessel (V) enters the Pacinian corpuscle, and approaches the end; it possesses a sheath which is the continuation of the peripheral capsules of the Pacinian corpuscle. $\times 100$. (Klein and Noble Smith.)



FIG. 217.—A touch-corpuscle from the skin of the human hand, stained with gold chloride.

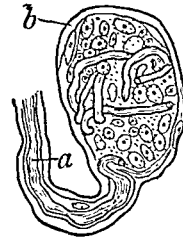


FIG. 218.—End-bulb of Krause. *a*, Medullated nerve-fibre; *b*, capsule of corpuscle.

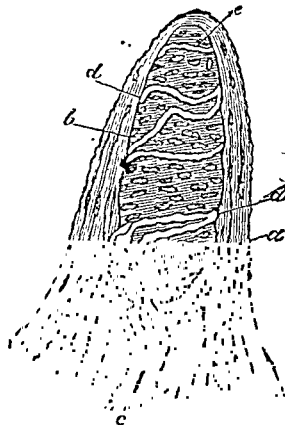


FIG. 219.—Papilla from the skin of the hand, freed from the cuticle and exhibiting a Meissner's corpuscle. Papilla treated with acetic acid; *a*, cortical layer with cells and fine elastic filaments; *b*, tactile corpuscle with transverse nuclei; *c*, entering nerve; *d* and *e*, nerve-fibres winding round the corpuscle. $\times 850$. (Kölliker.)

of cells cut off originally from the lower layer of the epidermis, and surrounded by a connective-tissue sheath. They do not occur in all the papillæ of the parts where they are found, and, as a

rule, in the papillæ in which they are present there are no blood-vessels.

The nerve winds round the corpuscle before it enters (fig. 219), then loses its medullary sheath; its axis-cylinder branches, and the branches terminate within the corpuscle.

Hairs are important organs of touch, particularly in the whiskers of the carnivora. Here a nerve network surrounds the base of the hair.

Merkel "Cells."—In some cases the nerve-fibrils within a stratified epithelium end in crescentic expansions (*tactile discs*) which are

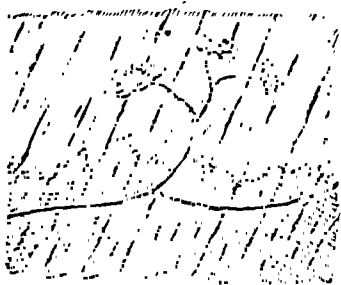


FIG. 220.—Termination of medullated nerve-fibres in tendon near the muscular insertion. (Golgi.)

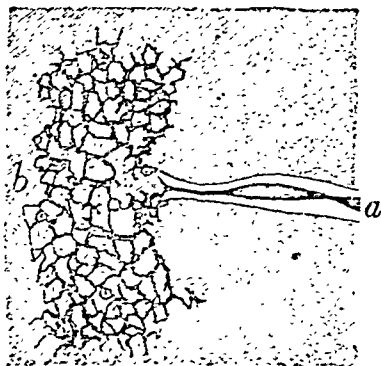


FIG. 221.—One of the reticulated end-plates of fig. 220, more highly magnified. *a*, Medullated nerve-fibre; *b*, reticulated end-plate. (Golgi.)

applied to the deeper epithelium cells. These are found in the skin of the pig's snout.

Free nerve-endings, *i.e.*, nerve fibrils which appear not to be attached to any specialised nerve-endings also are found. They occur in the skin and are considered to be responsible for pain largely because the cornea of the eye, which has free nerve-endings only, appears to appreciate little else but pain. There is evidence, however, that pain may be caused by the stimulation of other nerve-endings also.

In addition to the special end-organs, sensory fibres may terminate in **plexuses** of fibrils, as in the sub-epithelial and the intra-epithelial plexus of the cornea, and around the hair follicles in the skin generally.

Woollard has described unmyelinated nerve plexuses as occurring in the skin and many organs. They are probably concerned with diffuse pain.

Sensory Nerve-endings in Muscle and Tendon.—The sensory nerve-endings in muscle are not only concerned with conscious sensation but also with the reflex maintenance of posture and

equilibrium. The original description by Ruffini (1898) remains the best available. This function was first appreciated by Sherrington and worked out in detail by Matthews (1933).

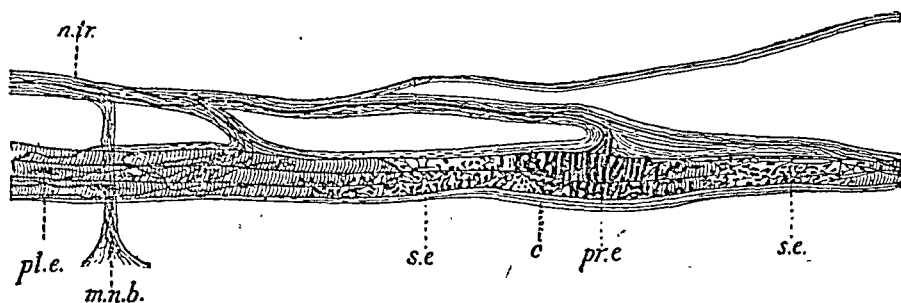


FIG. 222.—Neuro-muscular spindle. *c.*, Capsule; *n.tr.*, nerve trunk; *m.n.b.*, motor nerve bundle; *pl.e.*, plate-ending; *pr.e.*, annulo-spiral-ending; *s.e.*, flower-spray ending. (After Ruffini.)

They have now been differentiated into four distinct groups:—

1. The “flower-spray”-endings on the muscle-spindles. These look very much like end-plates, as pictured in figs. 220 and 221. They are length-recorders, that is, they register passive stretch but cease to record during active contraction.

2. The annulo-spiral fibres also on the muscle-spindles. This nerve-ending appears to be looped round a much nucleated intra-fusal fibre. They are also length-recorders, but have a higher threshold and therefore give off impulses only on very severe tetanus—or very severe stretch.

3. The tendon organs of Golgi. These record absolute stretch, produced actively or passively, not rate of stretch (fig. 220).

4. The nerve-endings in the fascia, etc. These are commonly Pacinian corpuscles which are also sometimes imbedded in the fleshy tissue of the muscle. A simpler and less frequent type is the Golgi-Mazzoni corpuscles, which are encapsulated but simpler than end bulbs which occur in tendons and also in the sheaths of tendons and muscle. These nerve-endings almost certainly respond to mechanical and pressure stimuli.

5. Free nerve-endings are also found in the connective tissue of muscle.

These endings are differentiated from muscle plates by the fact that they degenerate when the posterior roots are cut (Sherrington).

The Special Senses.

It must be realised that the eye and the ear, etc., are essentially highly specialised nerve-endings which, like those of the skin, are developed from the ectoderm or outer layer of the embryo. The details of their structure are considered later.

Cutaneous Sensations.

The surface of the skin is a mosaic of tiny sensorial areas; these areas are not set edge to edge as in the retina, but are separated by relatively wide intervals which are not sensitive to stimuli just above liminal intensity. If the stimuli are made nearly minimal, the individual fields are reduced to small spots. Each of these spots subserves a specific sense, touch, cold, heat or pain, and each doubtless coincides with the site of some special end-organ, placed either singly or in clusters. The "touch spots," "cold spots," "heat spots," and "pain spots" are intercommingled. In some districts one variety predominates, in others another. "Pain spots" are the most and "heat spots" the least numerous. It is a matter of common experience that the sensitiveness of these varieties of cutaneous sensation differs in different parts of the body. The tip of the finger, which is very sensitive to the true tactile sense (sense of pressure or contact), is not nearly so sensitive to alterations of temperature as the forearm or cheek, to which a washerwoman generally holds her iron when forming a judgment of its temperature. Some parts are more sensitive to pain than others, and in the cornea we have a surface in which "pain spots" alone are present.

For the more accurate exploration of the skin, *æsthesiometers* of various kinds have been invented. The sense of pressure may be estimated by the ability of the skin to distinguish different weights placed upon it; there must be no lifting of the weight, or the motorial sense is brought into play. The fraction which by Weber's law represents the differential threshold (see p. 652) varies from $\frac{1}{36}$ to more than $\frac{1}{16}$ in different parts of the body. It does not, however, follow that the acuteness of the pressure sense varies exactly as the ability of accurately localising sensations; for instance, the skin of the forearm is as sensitive to pressure changes as that of the palm; and the tip of the tongue, which is the most discriminative region of the body for locality, is not so for pressure. For pressure stimuli which are near the limen or threshold of sensation, the hair *æsthesiometer* is much used; this is a hair suitably mounted in a holder; the hair can then be shifted backwards or forwards in the holder, and the amount of pressure it exercises can thus be varied. It is used for the exploration of "touch spots," and these are found most numerous around the hair follicles. The touch spots are more numerous in some parts than in others, but fifteen for each square centimetre of skin is a rough average. To explore "pain spots" a stout hair or needle is used; in the latter case the needle shifts up and down in the holder, and works against a spring which registers the amount of pressure exerted to

evoke a painful sensation. The sensation evoked by a "pain spot" is unaccompanied by "cold" or "heat," even if a cold or hot needle is used. For the exploration of "heat spots" a small, hollow, metallic pencil is kept warm by a stream of warm water; this is moved over the surface; at the site of the "heat spots" the pencil will feel peculiarly warmer. "Cold spots" can be similarly mapped out by the use of a cold pencil. The next figure (fig. 223) shows the distribution of hot and cold spots on the back of the

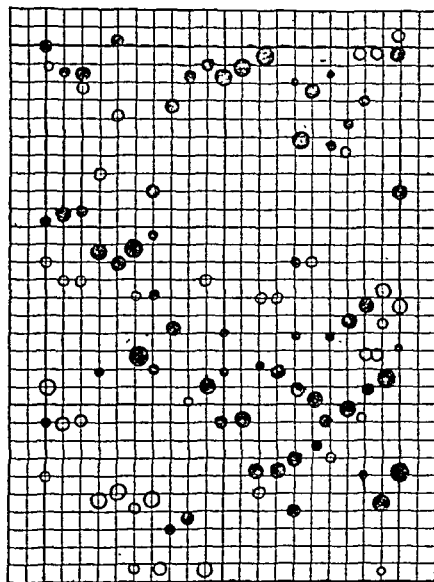


FIG. 223.—Heat and cold spots on a sq. cm. of the back of the hand.
(Somewhat enlarged. After Donaldson.)

The black dots represent cold spots, their size indicating the strength of the reaction; the circles represent hot spots.

left hand. Certain drugs if applied locally, *e.g.* menthol, stimulate the cold spots only.

All these facts clearly indicate that different varieties of sensation are the result of the stimulation of different end-organs, and that the impulses are conveyed to the central nervous system by different groups of nerve-fibres; they moreover form the clearest piece of evidence we have that pain is a distinct kind of sensation.

The question is more difficult to answer, which particular end-organ is concerned with each variety of sensation? There is, however, little doubt that the nerve-fibrils around the hair follicles of the short hairs are the terminations most affected by changes of pressure, and also that Meissner's corpuscles are purely tactual, taking the place of hairs in hairless parts. In the palmar surface of the last phalanx of the index finger, there are 21 Meissner's

corpuscles per square centimetre; in other parts of the palm and sole the number varies from 2 to 8. End-bulbs are believed to be the organs for cold; they are most numerous in the conjunctiva and glans penis, where "cold spots" are almost exclusively present. The end-organs in "heat spots" have not been identified with certainty, but the corpuscles of Ruffini are considered to be such, as they are correlated with the warm spots.

As compared with the sensation obtained from pain spots, touch is quicker in both development and subsidence. Thus vibrations of strings are recognisable as such by the finger, even at a frequency of 1500 vibrations per second. A revolving wheel with a toothed edge gives a sensation of smoothness when the teeth meet the skin at the rate of from 480 to 640 per second.

The Nervous Connections of the Skin of the Hand.

In view of the special importance of sensation in the hand and fingers, the arrangement of the nerves to these parts has been investigated by Stopford, who has concluded as follows:—

1. Cutaneous sensory end-organs are connected with fibres which soon join the main deep nerves (median and ulnar) or which take part in the formation of the so-called purely cutaneous nerves (radial, lower external cutaneous branch of the musculo-spiral and the musculo-cutaneous).

2. The nerve-fibres from the subcutaneous sensory terminals are less regular and are arranged in groups.

- a. Tactile pressure and pressure pain appear to be subserved by fibres which accompany tendons and possibly blood-vessels, but they are also slightly dependent upon fibres which join the main deep nerves or others which enter into the formation of the purely cutaneous nerves.
 - b. The recognition of posture, passive movement and tactile localisation are subserved by the digital branches of the ulnar and median nerves and fibres which assist in the formation of purely cutaneous nerves, particularly the radial.

CHAPTER XLVIII

SENSATION

IN discussing the general functions of a nervous system we have noted that it is concerned with the collection of impulses due to stimuli which arise in the environment of the individual and from various parts of the body. A certain number of these impulses reach consciousness and give rise to sensations.

All sensations experienced normally depend on the stimulation by an appropriate stimulus of nerve-endings which are adapted to receive certain kinds of stimuli or to appreciate a special quality of the environment. These nerve-endings have, for the special stimulus for which they are adapted, a lower threshold than have the nerve-fibres themselves, and make it possible for a nerve impulse to be set up by a degree of stimulation which would not otherwise be effective. For example, a degree of pressure which would not affect the ulnar nerve (the "funny bone" of the elbow) will cause a sensation of touch if applied to the nerve-endings of that nerve in the little finger.

Nerve-endings have been developed for the appreciation of a large variety of stimuli, *e.g.* light and colour, sound, smell, pressure. It is convenient to leave the detailed study of these to later chapters, since in some instances, *e.g.* the ear and the eye, the specialised nerve-ending has become much elaborated.

The **stimuli** must not only have a special quality but must be of adequate strength. Too light a touch, too faint a sound, will produce no effect on consciousness. That strength of stimulus which just suffices to evoke a sensation is called the *liminal* (from *limen*, a threshold) * value of the stimulus, or its *absolute threshold*.

Similarly, the difference between two stimuli must not fall below a certain minimum in order that that difference may be appreciated. If two musical tones are of too nearly identical pitch, if two colours are of too nearly identical hue, the difference may be imperceptible. There is, therefore, a liminal value for a stimulus difference. This is known as the *differential threshold* of the stimulus.

* Strictly speaking, the liminal value is that strength of stimulus which, in a series of trials, as often just fails as it just succeeds in evoking a sensation.

Weber's law states that the just appreciable difference between two stimuli depends on the ratio of that difference to their magnitudes, and not on the absolute difference between their magnitudes. Fechner, after bringing forward further evidence in favour of the law, endeavoured to deduce from it the conclusion that the strength of a sensation is proportional to the logarithm of its stimulus; in other words, that the stimulus must increase in geometrical proportion for the sensation to increase in arithmetical proportion. Fechner's interpretation of Weber's law is, however, open to serious criticism, into which we cannot enter here.

Weber's law is but an expression of everyday experience. A rushlight will brighten a dark cellar, but its presence is unfelt in sunshine. So, too, if a room be lighted by 100 candles, and if one candle more be brought in, the increased illumination produced by the extra candle would be just perceptible to the eye. But if a room were lighted by 1000 candles, no appreciable difference would result from the introduction of an extra candle. Ten candles would have to be introduced, in order to effect a just noticeable difference. In each case a difference of one-hundredth of the original strength of stimulus is needful to cause a just appreciable difference in the sensation; and this is in accordance with Weber's law.

For light, the fraction is about $\frac{1}{100}$; for noise, it is about $\frac{1}{3}$; for cutaneous pressure, it varies between $\frac{1}{30}$ and $\frac{1}{10}$; for weight, between $\frac{1}{10}$ and $\frac{1}{40}$, in various parts of the body.

A sensation requires an appreciable time for its development. Part of this time is spent at the end-organ on which the stimulus acts, part in conveying the nervous impulse along the sensory nerve to the brain, and part within the brain itself. This *latent period* varies in length according to the sensation; e.g., it is longer for sight than for sound, and longer for pain than for touch.

The sensation outlasts its stimulus. Such *after-sensations* are particularly noticeable in the case of sight. We know, also, that unless the eye is stimulated for a sufficient length of time we do not see objects or movements.

The Impulse.—The evidence appears now to be complete that the nerve impulse is identical in nature in all nerves. The impulse set up in the optic nerve by light is the same as that set up in the auditory nerve by sound.

The difference in sensation recognised by the individual must be due to the "analysers" in the central nervous system. The impulses reaching certain analysers, such as those of sight, are interpreted as light however the impulse is set up. This was termed by Müller "*The Law of Specific Nerve Energies*." The term energy is a bad one, and is not used in a modern physical sense, but the law simply means that every sense-organ, however excited, gives rise to its own specific

sensation. However the retina or optic nerve is stimulated light is appreciated. Mechanical, chemical, or electrical stimulation of the chorda tympani causes a sensation of taste. These observations have been made during surgical operations.

A great deal of investigation of the action potentials which are the basis of the various kinds of sensation have been carried out by Adrian, Matthews, Bronk, Rijlant and others, using wireless valve amplifiers and oscillometers or cathode-ray oscillographs. In every case it is found that the stimulation of a receptor brings about a series of discharges which may vary much in their duration and in their frequency, from 5 to 300 per second. The more rapid the rise of intensity of the stimulus the greater the frequency of discharge. Thus the more rapidly the finger is pricked the

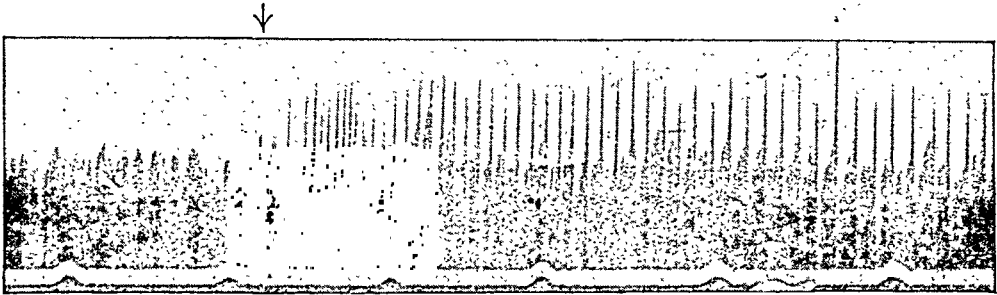


FIG. 224.—Record of current of actions from an afferent fibre from a muscle. At the arrow tension was placed on the muscle. Note the burst of impulses with some adaptation—which, however, is never complete—as shown by the continuance of the impulses. (Dawson.)

greater the sensation. The frequency and duration of the responses are different from different regions.

An interesting phenomenon is that of **adaptation**, in which it is found that if a stimulus is continued, impulses are no longer set up in the nerve. This is well shown in fig. 224. Thus is explained why a needle hurts while it is being inserted into the skin but not after it is in. This adaptation appears to depend on the end-organs concerned. In some, such as those of the skin, or Pacinian corpuscles, adaptation occurs rapidly, while in the nerve-endings of muscle it is very slow, a fact which no doubt permits the muscle when subjected to prolonged stretching to send out the sustained impulses so important in posture.

Intermittent stimulation, as might be expected, reduces adaptation. For example, although the response for a single blast of air on the skin is over in $\frac{1}{5}$ second, intermittency not exceeding 200 per second will maintain a burst of impulses at that rate. This is important in relation to the importance of air movement in ventilation.

Adaptation is seen in many of our common sensations. The same room feels warm to a man who enters it from the street, and cold to

another who has been in a conservatory. The hot bath appears to get more rapidly cooler than it actually does, while if one hand is placed in cold water and the other in hot, water at body temperature may appear warm to one hand and cool to the other. Herring calls the point of adaptation to temperature "the physiological zero." Thus the temperature of the mouth and the lips may actually differ by several degrees, yet neither of them will feel hot or cold because each is at the physiological zero temperature. Sensations of warmth or cold arise when the physiological zero is altered: they persist until a new zero is formed; according to Rivers and Head, adaptation to temperature is impossible when epicritic sensibility is absent. So, too, heavy weights feel unduly heavy after light weights, and *vice versa*. When false teeth or spectacles are first worn, their contact is well-nigh unbearable; yet later, through adaptation, the discomfort vanishes.

The impulse when set up passes into the central nervous system by means of **afferent nerves**. In the case of the cranial nerves, some are wholly sensory. In the case of the trunk and limbs, the impulses pass along fibres which become incorporated in mixed nerves and pass into the spinal cord by way of the posterior roots. Some of the impulses bring about, as we have seen, reflex movements, and may never reach consciousness, *e.g.* the impulse set up by slight pinching of the finger during sleep. The majority of the stimuli, however, during the waking hours and even during sleep, are strong, and the impulses which they generate pass up the spinal cord to the brain (see Sensory Pathways).

Impulses from Muscles.—Investigations (Matthews) tend to show that there are characteristics of discharge corresponding to the four classes of nerve-endings already described, but we do not know with certainty which come from which, nor what functions each subserves, but we know that, in addition to afferent impulses which are appreciated as pain in muscle, there must be those which are concerned with the appreciation of length and tension. An interesting point is the fact that the impulses from an extensor muscle of a decerebrate animal in rigidity cease when the muscle is caused to contract more actively.

A single sense-organ in a muscle has been found to set up impulses with a frequency of 30 per second. This has been discovered by using the sternocutaneous muscle of the frog, and by successively cutting off fibres to leave only one muscle-spindle. There is an increase in the frequency of the impulses with the logarithm of the load and frequencies from 5 to 500 have been recorded. There is, as we have said, little adaptation to stretching.

Impulses from the Skin.—These are characterised by being of very short duration, about 0.2 sec., and the nerve-endings of the

skin becoming very rapidly adapted, as the adaptation to skin sensation suggests. Pain from section of the skin is therefore short-lived unless the injured part is stimulated further by movement.

Impulses causing Pain.—Pain is experienced from stimulation of any sense to excess, but most commonly when there is actual damage to tissue by severing or burning of the skin or from excessive tension or oxygen-want of internal tissues.

There has been considerable debate as to whether or not there are special nerve-endings, for in addition to the variety of stimuli which may bring about pain, it has been pointed out by Herring that it would be rather remarkable if there were special endings in internal tubes such as the ureter, from which there is normally no sensation at all. On the other hand, in certain regions of the body, *e.g.* the cornea, where there are no specialised nerve-endings but only the terminal ramifications of nerves, pain is felt, while it has long been known that there are pain spots in the skin which are sensitive only to pain. As we shall see, too, it is well established that in the cord the fibres carrying pain (like touch and temperature) become collected into distinct bundles or tracts. This subject owes much of recent years to the work of Adrian in Cambridge.

The difference between touch and pain is seen when a needle is placed on the paw of an anæsthetised animal and forced into the skin, the action potential being recorded from the nerve to the part. When the paw is touched there is a short burst of impulses, but when the paw is pricked there is a much longer burst of impulses. Both types of stimulus show adaptation but pain less than touch. The frequency of the discharge for pain may vary from 5-100 per sec. It is not uniformly high as it would be if it were due to stimulation of any kind of receptor.

It seems likely that the *extent* of the sensation is determined by the number of fibres thrown into activity, but the *intensity* of the sensation depends on the frequency of the discharge set up. As we shall see later, the interpretation of the nature and the value of the stimulus to the animal depends on the cerebral cortex, but as seen in the spinal reflex harmful stimuli are at once acted upon by the spinal cord. The evidence would appear to indicate that while there are special receptors for pain, the excessive stimulation of other sensory impulses may produce a gross disturbance analysed as pain. This would obviously have the advantage of protecting the sensory endings concerned, as in the case of light, for looking at the sun may cause detachment of the retina. Adrian concludes that "it is probable that there are no hard-and-fast divisions into pain endings and touch endings or free endings and encapsulated endings," but thinks there is no doubt that the pain endings are mainly free and that few of the encapsulated endings give rise to pain.

It would seem, too, that the stimulus for pain must attain a certain massiveness before it produces a sensation, whether it is stimulating a free nerve-ending or a nerve-ending subserving some other sense.

Pain in muscle is of special interest as it arises in the cardiac muscle and the evidence is very complete that it is due to ischæmia or lack of blood supply to the muscle. The pain which occurs in cramp or muscle spasm is thought to be analogous. Pain which is produced by cutting off the arterial supply to the arm with a sphygmomanometer cuff does not appear to depend on the tension in the muscle, for it is not accentuated by contraction although it

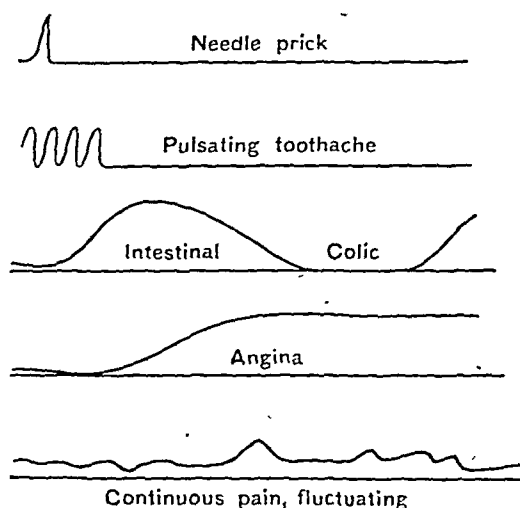


FIG. 225. (Lewis.)

is related to its total amount. It is, however, at once relieved by release of the circulation. This has led to the suggestion of Lewis that a *P (pain) substance* is released, and it seems probable that the sensation of fatigue in a muscle is produced by a similar if not identical substance. The close association between lactic acid and fatigue suggests that this may be the substance concerned.

Pain is affected by a variety of circumstances which may alter its character. One burst of impulses is appreciated as a single stab of pain, such as that of a pin prick. If tension is produced by the accumulation of pus in a confined space, such as the socket of a tooth or in a finger, the arterial pulse may be communicated to the nerve-endings and the pain assumes a throbbing character. If the tension is produced by peristaltic waves the pain is intermittent, such as that produced by taking a purgative, or by the passage of a stone down the bile duct or the ureter. This pain is known

as colic and its intermittence. is an important point in diagnosis. Much pain, especially that following injury, is aggravated by movement. The pain which results from arterial blockage is sustained while neuritic pains from inflammation of nerves tend to be irregular. These various types of pain may be shown diagrammatically as in the above figure from Lewis, a research physician at University College, London, who has done much to elucidate the problems of sensation and circulation in the human skin. Adrian (1928 and 1932); Leriche (1938); Lewis (1943).

Classification of General Sensation.

Sensation may be conveniently divided into Special Sensation and General Sensation. The former is that which is appreciated by highly specialised nerve-endings localised in certain parts of the body, *e.g.* the nose, ear, eye, tongue. The latter is not so confined.

General sensation is that felt by the body generally; it may be superficial, *i.e.* that from the skin, and deep, *i.e.* that from the underlying structures. If the nerves to the skin are cut, deep sensation remains. Superficial sensation includes touch, pain, and temperature. Deep sensation refers to the appreciation of pressure (as distinct from touch), of movement or pain in muscles and joints. The fibres subserving this sense run with the muscular nerves, and accompany blood-vessels.

Both superficial and deep sensations have been subdivided further according to their fundamental nature.

Our knowledge of this subject owes much to the pioneer work of Head who cut one of the nerves in his own arm, and, in conjunction with Rivers, noted accurately the date and other particulars of return of function. The first sensations returned about the eightieth day after the operation; they are termed by him *protopathic*. Protopathic sensibility depends on definite specific end-organs distributed over the skin as sensory "spots," viz., heat, cold, and pain spots. When this sensibility is alone present, the spaces between these spots are insensitive to cutaneous stimuli; the heat spots react only to temperatures above 37° C., the cold only to temperatures below 26° C.; the sensation radiates widely, and is often wrongly localised. The tactile sensations of the skin, the intermediate temperature sensations, the power to localise them accurately, the sensibility of the spaces between the spots, and a more refined sensibility to pain, return much later, and this *epicritic* sensibility is not perfect until many months after regeneration has started. It is not known whether protopathic and epicritic impulses are subserved by the same or by different nerve-fibres.

Stopford has investigated deep sensibility and has found that, like cutaneous sensibility, it returns in two stages after division and suture of a peripheral nerve. A first stage consists of the recovery of the ability to appreciate a pressure contact and the pain induced by excessive pressure, and a second stage is demonstrated by the return of the power to localise accurately a pressure stimulus and recognise the position and passive movement of a joint. Stopford points out that the elements of sensation included by Head under the term protopathic sensibility and those of stage one in deep sensibility are fundamentally protective in function and make their appeal to the thalamus which we know is capable of appreciating crude sensation; whilst those in epicritic sensibility and stage two of deep sensibility include the higher and discriminative aspects of sensation which are dependent upon the sensory cortex. In consequence he suggests the following division of sensation—

A protective system, composed of the protective elements of sensation, in which recovery occurs early and is more complete, after suture of a peripheral nerve.

Concerned with the recognition of:—
 (a) Pain (whether induced by prick or excessive pressure).
 (b) Extremes of temperature.
 (c) Tactile pressure.

A discriminative system, composed of the discriminative elements of sensation, in which recovery occurs at a later time and is less complete.

Concerned with the power of:—
 (a) Tactile Localisation.
 (b) Tactile Discrimination.
 (c) Recognising position and passive movement.
 Recognition of fine differences of temperature.
 Appreciation of the lightest touch.

Such a subdivision of sensation is supported by researches in comparative anatomy and is in accord with our knowledge of the evolution of the nervous system. We have already observed that protective reflexes take precedence over those more recently acquired and that they do not depend on the cortex. (See The Plantar Reflex.)

Nevertheless, divisions of sensation such as those advanced by Head and Stopford have been criticised by a number of observers who have made human experiments, such as Trotter and Davies, who divided as many as seven of their cutaneous nerves, and Boring who severed only a small branch of a nerve. Later, Sharpey-Schafer contrasted by experiments on himself the recovery after division and crushing of corresponding peripheral nerves (posterior branch of the internal cutaneous nerve of each arm). The nerve severely crushed recovered much more rapidly than that cut. He also emphasised the occurrence of a stage, hyperæsthesia or excessive sensibility to pain, which accompanies the feeling of numbness and lessened sensibility to touch, warmth, and cold. Similar

hyperæsthesia has been noticed by most other observers at the edge of any paralysed area. Sharpey-Schafer suggested that the term "protopathic" is nothing more or less than pain, and that the hyperæsthesia is probably caused by the growing parts of the nerve-fibres which subserve pain being hypersensitive. These correspond to the protective system of Stopford.

Whilst it is not wise as yet to be dogmatic in regard to the division of sensation, it does appear that the evidence from both clinical experience and comparative anatomy supports strongly the main views of Head and Stopford, and their conclusions do seem to explain the facts.

Stopford has given us a convenient view of sensation as a whole. He points out that at first there is evolved a crude mechanism for protection against a harmful environment; later on, better perception and powers of discrimination are developed. These functions are intimately related to the acquisition of better motor control and vision, and, later still, with the expansion of the cerebrum an increasing understanding of tactile perception is created. It must however be understood that each higher stage overlaps, reacts upon, and modifies the lower one.

Drugs.—Cocaine applied locally depresses all forms of cutaneous sensibility, but especially the true tactile sense; carbolic acid acts similarly but less strongly. Chloroform produces a temporary burning sensation, and then blunts sensibility, especially to temperature changes. Menthol produces a feeling of local cold because it first causes hyperæsthesia of the end-organs for cold; this is followed by a depression of the activity of these organs, together with that of those subserving other forms of cutaneous sensation.

CHAPTER XLIX

THE SENSORY PATHWAYS

Grouping in the Spinal Cord.—When the impulses underlying sensation reach the spinal cord by way of the posterior roots (see p. 662), they are sorted out according to their origin and are carried up the cord by bundles of fibres, each bundle being responsible for a particular sensation. These bundles are known as the *sensory tracts*. With the exception of the posterior columns of Goll and Burdach, which we have seen are composed of axons of cells in the posterior ganglion, the ascending tracts are the axons of cells in the neighbourhood of the posterior horn (*substantia gelatinosa* of Rolando and in Clarke's column).

Muscle and Joint Sense.—By this sense we become aware of movement and of the position of the limbs. The efficiency of this sense can be gauged by the power of the individual to place one limb in exactly the same position as the other although the eyes are closed. Muscle sense depends on the degree of compression of the sensory nerve-endings or muscle spindles in the muscles and the analogous endings in tendons. Through this sense not only do we become aware of muscular movement, but also by the help of related associations we estimate weight. The appreciation of weight does not depend on impulses of cutaneous origin, since it is retained in an individual whose skin has been rendered insensitive by cocaine or by disease.

We have already remarked in relation to the cerebellum that all the impulses which arise in the muscle do not reach consciousness. Those which are concerned with posture and equilibrium pass up in the cerebellar tracts to the pons, mid-brain, and cerebellum (see p. 662).

The impulses which do reach consciousness pass into the central nervous system by the posterior nerve-roots and pass at once *via* the columns of Goll and Burdach, *i.e.* the *fasciculus gracilis* and *fasciculus cuneatus*, in the posterior part of the cord of the same side, to the nucleus gracilis and nucleus cuneatus in the medulla. Thence they are relayed by other neurones to the thalamus of the opposite side, the actual crossing taking place at the decussation of

the fillet in the upper part of the medulla. A few fibres pass to the cerebellum of the opposite side. The column of Goll is derived from the posterior roots of the sacral, lumbar, and lower thoracic roots, but becomes displaced to the middle line by the column of Burdach from the upper spinal roots.

Vibratory sensation, *i.e.*, appreciation of vibrations such as those of a tuning-fork, has a similar pathway. The receptors appear to be situated in the bones.

Touch.—The nerve-endings concerned with touch appear to be the Meissner's corpuscles in the skin, and the Pacinian bodies for deeper sensation. The impulses of **tactile discrimination**, *i.e.*, the power of the individual to distinguish between adjacent points on the body surface, travel up on the same side of the cord in the posterior columns with the impulses of muscle and joint sense.

The impulses of **tactile localisation**, or power of localising a touch, on the other hand pass up the posterior columns, but *after a few segments* cross to the opposite side to occupy the anterior parts of the spino-thalamic tracts close to the fibres carrying impulses of temperature and pain.

The impulses of light touch, **tactile sensibility**, have a double pathway, some going with the impulses of discrimination, and some with those of localisation. In the mid-brain the bundles carrying the various forms of touch become somewhat separated, and a lesion may affect one variety without affecting the others.

Temperature and Pain.—The impulse in each instance begins at the nerve-ending.

The impulses are conveyed by the posterior root-fibres to the central nervous system, where they pass *almost immediately** to the more posterior part of the spino-thalamic tract of the other side of the cord. We know this largely from studying the disease syringomyelia, in which there is an enlargement of the central canal of the cord, due to degeneration of the surrounding nerve-tissue; the morbid process cuts across the decussating fibres and there results loss of tactile localisation and of sensations of pain, heat, and cold in the segments in the neighbourhood of the lesion, although tactile discrimination is unaffected (dissociated anæsthesia). In this condition, severe injury, such as burning of the fingers with a cigarette, may occur unknown to the patient. He may not let the cigarette drop as his muscle sense and tactile discrimination may be normal.

It must be understood that this consideration of the pathways for pain and temperature together is merely one of convenience. The impulses conveying the sensations are carried by different bundles, as is seen by the fact that certain lesions of the cord may

* The short lengths of this tract before they cross form Lissauer's tract.

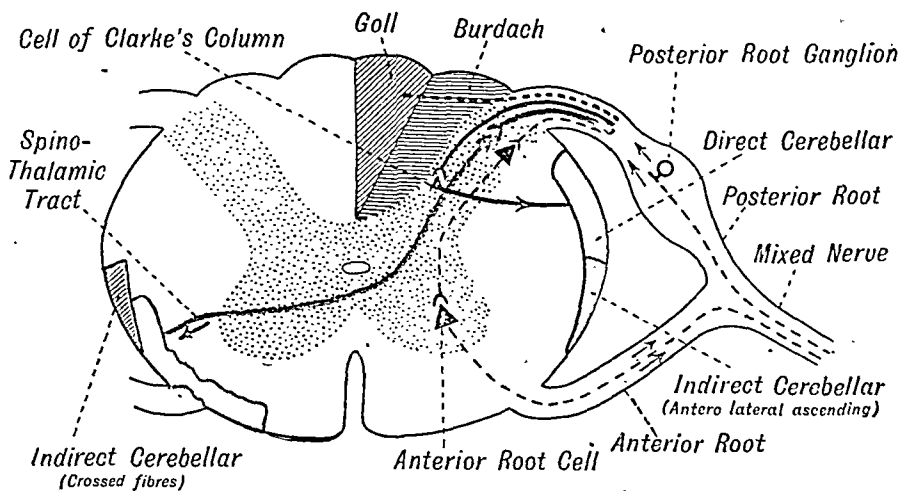
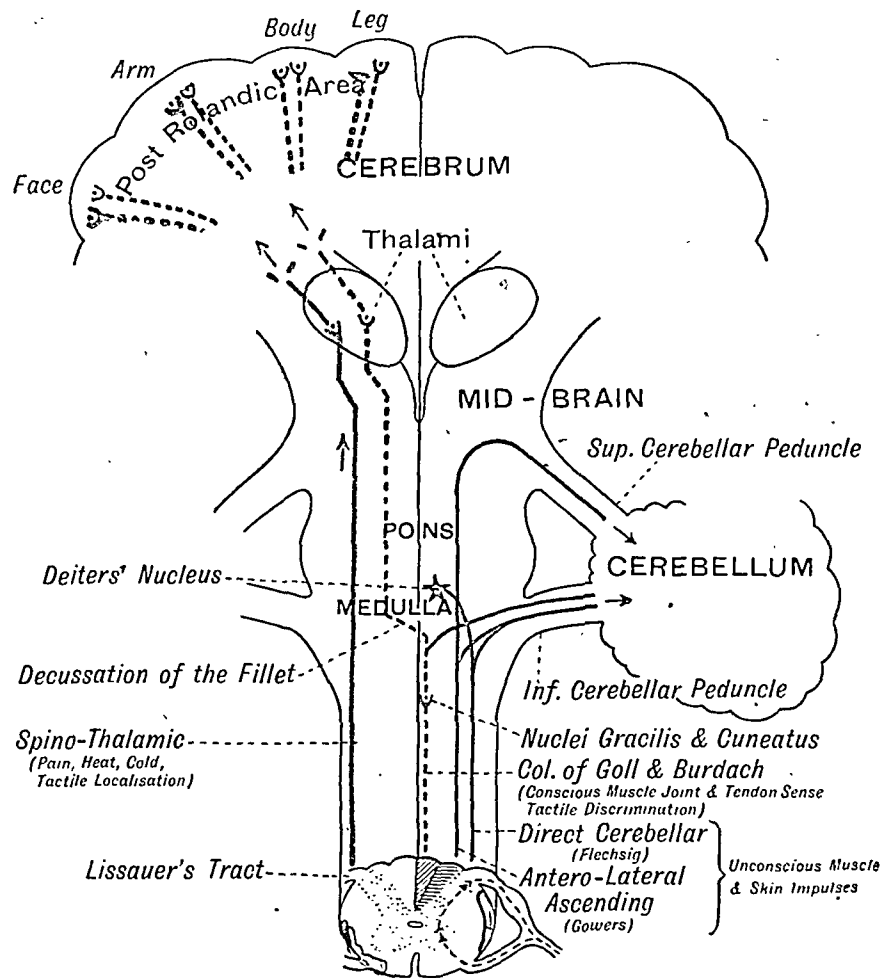


FIG. 226.—Main afferent paths in central nervous system.

abolish, for example, heat, and leave cold unaffected. Cutaneous and deep pain may also not be affected together, but this is probably explained by the fact that the subserving fibres do not enter by the same spinal roots (Stopford).

The actual fibres which subserve pain appear to be of all varieties (see p. 68). Some are small medullated fibres, but according to Ranson the majority are of the more primitive non-medullated type. They are very evident in sections of the nerves of the skin which we know has a high degree of pain sensibility. These observations indicate that pain is phylogenetically a most primitive sensation.

The Thalamus.

Eventually all the impulses of general sensation reach the ventral nuclei of the thalamus where they are felt indistinctly, but from which they are sorted out again and are distributed by way of the posterior part of the posterior limb of the internal capsule to the sensory area of the cerebral cortex.

The thalamus informs us if a body is hot or cold, but cannot differentiate more accurately between finer differences of temperature, nor can it tell the size or shape of an object. Similarly, the thalamus can appreciate only crude pain, which it cannot localise.

In cases of rupture of the thalamogeniculate artery which destroys the posterior third of the ventral nucleus there may be transient disturbance of cutaneous sensation and on the opposite side a permanent loss of deep sensibility.

The thalamus is also intimately connected with the various parts of the hypothalamus and corpus striatum (Le Gros Clark).

The lateral ventral nuclei receive fibres from the cerebellum and transmits to areas 4 and 6 of the cortex.

It is possible by injecting strychnine into the thalamus (Dusser, de Barenne) to demonstrate topographical localisation in it.

The Significance of Sensation.

It is an important physiological truth that the significance of any given sensation to any individual depends on the circumstances in which it is experienced or in which a similar sensation has been experienced in the past. This is simply demonstrated in the old experiment of Aristotle. If a pencil be placed between the crossed fore and middle fingers there is a sensation of touching two objects. The pencil is touched by two surfaces, which, under ordinary conditions, could only be touched by two separate objects, and in the light of past experience we conclude that two objects are involved, regardless of the fact that the fingers are crossed. Many other errors of judgment depend on similar past experience.

We may assume that minute areas of the body surface have each their *local sign*, i.e. the sensation arising from stimulation of one area differs in some obscure quality from the sensations arising from stimulation of neighbouring areas, thereby acquiring its own spatial colouring which enables us to identify the area when stimulated. The difference of local sign between two near points may be imperceptible in one region of the body, but fully recognisable in another. Again, the delicacy of the sense of touch may be very much increased by practice. A familiar illustration is seen in blind people, who, by constant practice, can acquire the power of reading raised letters, the forms of which are almost if not quite undistinguishable by the sense of touch to an ordinary person.

The extent to which two points of a pair of compasses can be discriminated varies appreciably in different parts of the body (Weber). A few results are as follows:—

Tip of tongue	$\frac{1}{24}$ -inch	1 mm.
Palmar surface of third phalanx of forefinger	$\frac{1}{12}$..	2 ..
Palmar surface of second phalanges of fingers	$\frac{1}{6}$..	4 ..
Palm of hand	$\frac{1}{2}$..	10 ..
Dorsal surface of first phalanges of fingers	$\frac{1}{2}$..	14 ..
Back of hand	$1\frac{1}{2}$..	25 ..
Upper and lower parts of forearm	$1\frac{1}{2}$..	37 ..
Middle of thigh and back	$2\frac{1}{2}$..	62 ..

In the skin of the limbs, it is found that before they are recognised as two, the points have to be further separated when the line joining them is in the long axis of the limb than when in the transverse direction.

The different delicacy of local signature possessed by different parts may give rise to errors of judgment in estimating the distance between two points where the skin is touched. Thus, if the blunted points of a pair of compasses (maintained at a constant distance apart) are slowly drawn over the skin of the cheek towards the lips, it is almost impossible to resist the conclusion that the distance between the points is gradually increasing. When they reach the lips they seem to be considerably further apart than on the cheek. Then, too, our estimate of the size of a cavity in a tooth is usually exaggerated when based upon sensations derived from the tongue alone.

When, as occurs under certain conditions, an object is adjudged different from what general experience teaches us to be its "real" character, we have an *illusion*. Thus a line or figure may appear to be longer or shorter than it really is, or to take a direction different from its real direction. Or a weight may appear heavier than another which is really equal to it. Illusions are due partly to peripheral, partly to central factors. Their investigation falls within the province of experimental psychology.

Similarly, it will be remembered that our estimations of size are commonly dependent on experience. We presume, for example,

that lamp-posts do not change in size in the same street. A drawing of a street, therefore, in which the perspective is wrong in relation to the lamp-posts may give a completely erroneous idea of relative sizes.

The significance of a sensation also may depend on immediately previous sensation. For example, water at 30°C . is hot to a hand which has previously been in ice-cold water but is cold to a hand which has been in water at 50°C .

Psychological Set in Pain.

When the physiologist has finished considering pain the psychologist takes the matter further and his rôle is of the greatest importance in practical medicine. The psychological set is important in both negative and positive directions; that is to say, a severe injury may be received in certain circumstances and not produce pain, or pain may be felt when there is no discoverable abnormality to account for it.

Absence of pain is frequent if the injury, such as a severe kick on the shin, is received during an exciting game of football, but still less understandable is the fact that a patient may be persuaded, especially during hypnosis, that any given procedure is or is not painful. In hysteria a patient may be convinced that she cannot feel in some part of the body and allow herself to be injured, yet the doctor may, from the anatomical distribution of the anæsthesia, be quite satisfied that it is mental. Typical is glove anæsthesia, affecting the hand only, and which could only be produced by damage to all the sensory nerves at the wrist. Such patients are often tricked into recovery. It is believed that the state is essentially one of auto-suggestion. The subject is discussed in works on Psychology.

Referred Pain.—It is evident that the impulses which pass up certain paths have a certain significance. This we have already referred to in relation to reflexes. For example, an individual who has had a leg amputated may experience pain in the limb that is off if the nerve-fibres which formerly supplied the leg are stimulated through involvement of their cut ends in the scar.

Thus also pain, if set up by impulses which are transmitted by the sixth dorsal root, is referred to that part of the body from which we have had previous sensory experiences, namely the shoulder-blade, although in reality it may arise from the passage of a gall-stone down the bile-duct. Each spinal nerve contains afferent fibres from an internal organ as well as from the skin and errors in the localisation of disease on the part of the patient may readily occur. Commonly, however, as soon as the patient realises that pressure with the hand in a certain region elicits the pain, the latter is

no longer referred to a superficial area but to the organ lying underneath.

In connection with the question of referred pain, we must mention the pathological condition known as *allocheiria*; when the skin sensations in any given area are depressed, stimulation of that area may give rise to sensations which are referred to the corresponding area on the other side of the body.

Conditioned Pain.*—Any movement which in the past has been associated with a painful stimulus may cause a reaction like that of the painful stimulus. A threatened pin-prick may cause a reaction, *e.g.* of the circulation, like that of an actual pin-prick. (See Effect of Higher Centres on Circulation.)

It looks as if a process of "conditioning" was possible in relation to sensation since every sensation may acquire a significance which may bear little or no relation to the elementary quality of the sensation. The subject is closely related to conditioned reflexes but has been little investigated.

These facts are of great importance in disease. For example, pain on movement may have been associated with an injury, but the movement may continue to cause pain long after the injury has been recovered from. This state is seen also in pet animals.

Hyperalgesia and the Nocifensor System.

It has been pointed out by Lewis that when the skin is pinched in a few minutes there develops around the point an area of hyperalgesia or local tenderness of the skin associated often with a slight sensation of burning. He put forward much evidence that the fibres concerned belong to a peripheral arborisation of posterior root-fibres which differ from those of pain. Such arborisations have been found to overlap very appreciably but the hyperæsthesia is distributed in the area of a peripheral nerve distribution. It is argued that the fibres are different from those of pain because pain sensation disappears sooner than the hyperalgesia if the area is asphyxiated and particularly because pain sensations are necessarily more localised than the hyperalgesia which is diffuse.

Visceral Sensations.

Accurate and discriminative sensibility of varying nature is a special characteristic of the cutaneous area. Less elaborate sensibility is found in other parts also, but in most internal structures of the body it is limited to pain. The œsophagus and anal canal alone seem to be endowed with the temperature sense; the feelings of warmth

* So far as the author is aware this term has not been used elsewhere.

and cold on swallowing liquids of different temperatures are entirely referable to the upper portion of the alimentary canal. Hurst's experiments place this beyond question; immediately the food has passed into the stomach we are unaware of its temperature except by the warming or cooling of the neighbouring portion of the gullet, or the skin overlying the viscera.

Pain is the most widely distributed sense in the body, but in internal organs is not localised accurately, and it is here that the "referred pains" in corresponding skin areas (see p. 666) are useful for diagnostic purposes. Pain, however, is not produced in the viscera by handling or even by cutting or burning: it appears to be associated with excessive action, stretching, and with inflammatory conditions which involve the sensitive *parietal* layer of the peritoneum. This has been amply shown in operations in which the abdomen has been opened under local anæsthesia. Inflammation of the serous membranes is an exceedingly painful condition—for instance, in pleurisy and peritonitis—but this condition, *per se*, does not apparently cause any referred pain or tenderness in cutaneous areas.

Many of these facts may be illustrated by the use of the spinal animal in which painful stimuli produce reflex movements of the limbs and tail. They also cause a dilatation of the pupil in the cat under chloralose anæsthesia. McDowall has shown that either of these methods may be used for tracing the afferent fibres from the viscera.

It appears to be a general rule, as Head first pointed out, that the mind projects sensations arising from an area of low sensibility to that area of higher sensibility which is related to it most closely by connections within the central nervous system, and this underlies the causation of referred visceral pains, and of allocheiria.

There are, however, special kinds of sensation arising from internal viscera which have no counterpart in the sensations of the cutaneous surface. Of these, hunger and thirst are the most familiar.

REFERENCES TO VISCERAL SENSATION :—Lewis, Leriche, Ranson, Morley.

Hunger.

When slight, hunger is termed *appetite*, and there is some difference of opinion whether the two are separate sensations, or only different in degree. Appetite is referred to the stomach, and is a normal sensation, which arises at an interval after a meal, and as is well known it is intensified by muscular exertion, especially if the air is cool. It has been suggested that the oxidation processes which occur in the muscles produce some substance or substances which excite the sensory nerve-terminals in the stomach. In

diabetes, where oxidation runs an unusual course, carbohydrates escape oxidation to a large extent, an intense appetite may be present in spite of abundant feeding.

Hunger is associated with motor activity of the stomach, which can be recorded from a swallowed balloon attached by means of a tube to a recorder. Carlson, Professor of Physiology in Chicago, claims that these movements bring about hunger pains. The sensation of hunger can be temporarily appeased by filling the stomach even with indigestible or non-nutritious material. Carlson has shown that the movements are reflexly inhibited when food enters the mouth and is masticated; the nerves of taste act as the afferent channel for the reflex; hence the feeling of hunger passes off long before absorption of food begins. It may be assumed that the appeasing of the appetite results in a reduction of gastric tone. There is evidence that the sense of hunger may be related to the amount of the blood-sugar (Lawrence). Attention was drawn to this aspect of the question by the fact that the injection of insulin which lowers the blood-sugar causes a sensation of hunger which may almost amount to pain. At the same time there are hunger contractions. These are inhibited by the intravenous injection of sugar (Bulatao and Carlson). An extensive study of two diabetic students who took insulin regularly, and in whom balloon records were taken from the stomach, failed, however, to reveal any relationship between the sensations, blood sugar and stomach movements (McDowall). The subject was investigated by Poulton and his co-workers, who showed that the actual pain occurs not when the stomach is contracting but when it is relaxed. Their experiments suggest that there is during hunger a rise of tension in the stomach or elsewhere which compresses the nerve-endings. These, however, are relieved when the muscle-fibres take up the tension and prevent the compression. This explanation receives support from the common experience that a pang of hunger is frequently associated with the sound of gurgling and sensations of movement of gas in the gut.

It is just possible that the sensation due to slight gastric distension of an empty stomach by gas or a balloon is not the same as true hunger pain.

We must, however, recognise that the gastric sense is a complex one, as is illustrated by the aversion for food felt during monotonous diets or after over-feeding, or when certain articles of diet are taken, or the cause of the absence of hunger after fasting for four days. These and many other points are not as yet understood. (Carlson, Poulton.)

Thirst.

Thirst is a sensation referred to the pharyngeal region rather than to the stomach, and appears, like hunger, to be a protective signal, locally excited to warn the living organism of the necessity for regularity in the intake of nutriment. Although its intensity increases with the loss of water from the body, leading to a lessening of the saliva secreted, probably as a result of a slight increase in the osmotic pressure of the blood, it occurs normally long before there is any serious upset of the normal relationship of the water percentage of the tissues. It is appeased immediately by the administration of fluid, and although fluids reach the absorbing surface of the duodenum sooner than was formerly supposed to be the case, it is unquestionable that the relief of thirst is mainly the result of moistening the local surface, the impulses from which excite the sensation. Thirst may be produced by drying the throat artificially. This accounts for the thirst which results from the taking of excessively salt or sweet articles of diet. Mere physical drying of the throat (Cannon's "false thirst") produces a similar sensation and is relieved by the local application of water without its necessarily being swallowed. A further proof of the local nature of thirst is seen in the fact that it is abolished by painting the back of the tongue with cocaine, a drug which paralyzes nerves and nerve-endings. Thirst which is due to prolonged deprivation of water is not a mere local sensation, but is produced by loss of water in the tissues generally, exciting widespread sensory terminations therein; the bodily and mental anguish experienced are then of an intense character.

The independence of the two sensations hunger and thirst is well illustrated in many diseases, where a loss of appetite occurs without any corresponding loss of desire for fluid. Starling (1909).

CHAPTER I

THE PHYSIOLOGY OF CONSCIOUS STATES

Consciousness.

IN physiological considerations of sensation and voluntary movement it is usual to take consciousness for granted for we are far from understanding its exact nature. Consciousness belongs academically to the realm of Psychology, but it is becoming abundantly clear that there is no hard and fast line between the subjects of Physiology and Psychology. In considering the protective reflexes and also the conditioned reflexes, by which animals learn by experience, we have seen a whole host of activities which the uninitiated might have thought to be dependent on consciousness. We have seen that although consciousness may be necessary for the establishment of such conditioned reflexes, it is certainly not necessary for their operation once they have become "fixed" in the nervous system, and we can certainly learn without conscious effort, as in the case of advertising posters.

Consciousness may be defined as an awareness of the existence of oneself and of the external world, and the evidence is very complete that it is dependent in man on the occurrence of a given amount of oxidation taking place in the cerebrum. Without such chemical changes we know that nerve-cells cease to function and die. We can say, from a study of the changes in electrical potential of the brain, that consciousness is a correlate of the activity of cerebral nerve-cells, and we are aware of certain streams of impulses which pass through the cerebrum provided they are of sufficient magnitude, whether they occur during the awake or sleeping state. If they are present when we are asleep a dream results, but then we are not completely aware of our immediate environment.

It seems most probable that the state of consciousness varies throughout the animal kingdom, but in man alone has reached a stage of evolution which makes it possible to form mental concepts of which that of mind, as an abstract or spiritual entity, is the most important. The emotions appear, for the most part at least, to depend on instinctive drives very akin to reflex actions, and it is evident that many of the responses to such emotions are conditioned like reflexes. How conditioning, the emotions, and the

activities of the mind are correlated and affect feelings and conduct are discussed in *Sane Psychology*, a biological introduction to Psychology by the same author and publisher as this book.

In the past the subjects of Physiology and Psychology have been almost poles apart because those whose outlook commenced with the immaterial entity, mind, could see little or no need for the nervous system or any of its workings. It is, however, slowly becoming apparent that not only has mind a profound effect on body but the body greatly influences mental processes, and that many of the known workings of the lower parts of the nervous system have obvious counterparts in the mental plane, with the result that with a saner and more balanced appreciation of the facts the boundaries between Psychology and Physiology are fast disappearing and their separate fields are becoming merely conventional. Thus we have for the physical protection of the body, protective reflexes, protective instincts, and protective reasoning, all merging into each other, but all having a common purpose, while in Psychology we learn of many mechanisms for the promotion of the protection of the peace of mind.

Loss of Consciousness.

Although we do not know exactly what consciousness is, we know that it depends on a number of entities which are of great importance in practical medicine.

1. **The Physical Integrity of the Brain.**—We know that if the cerebrum is damaged extensively, consciousness is lost. This loss may be temporary and may result from a sudden blow, such as the “knock-out” in boxing. This is believed to be due to a sudden raising of the pressure in the cerebrum and the production of cerebral anaemia. (Trotter, Soutar.)

2. **The Oxygen Supply to the Brain.**—Any condition which reduces the oxygen supply to the brain produces unconsciousness. The oxygen may fail because the blood supply is deficient or the blood itself may not contain sufficient oxygen.

Loss of consciousness, therefore, occurs whenever there exists any condition which interferes with proper aeration of the blood in the lungs. If the blood is deficient in hæmoglobin, or if the hæmoglobin is combined with carbon monoxide to a sufficient degree, unconsciousness is produced.

A state of semi-consciousness may be produced by over-breathing. In this case the blood contains sufficient oxygen, but the loss of carbon dioxide prevents it from dissociating to the cerebral cells, and this is accentuated by any procedure which tends to lower the arterial blood-pressure, such as expiration against resistance (Hemingway).

A large variety of procedures and circumstances may produce a failure of the cerebral circulation. It may be produced by compression of the carotid vessels* (a dangerous procedure), a fall of blood-pressure such as results from hæmorrhage or from loss of the normal activity of the vasomotor centre, all of which cause a rapid loss

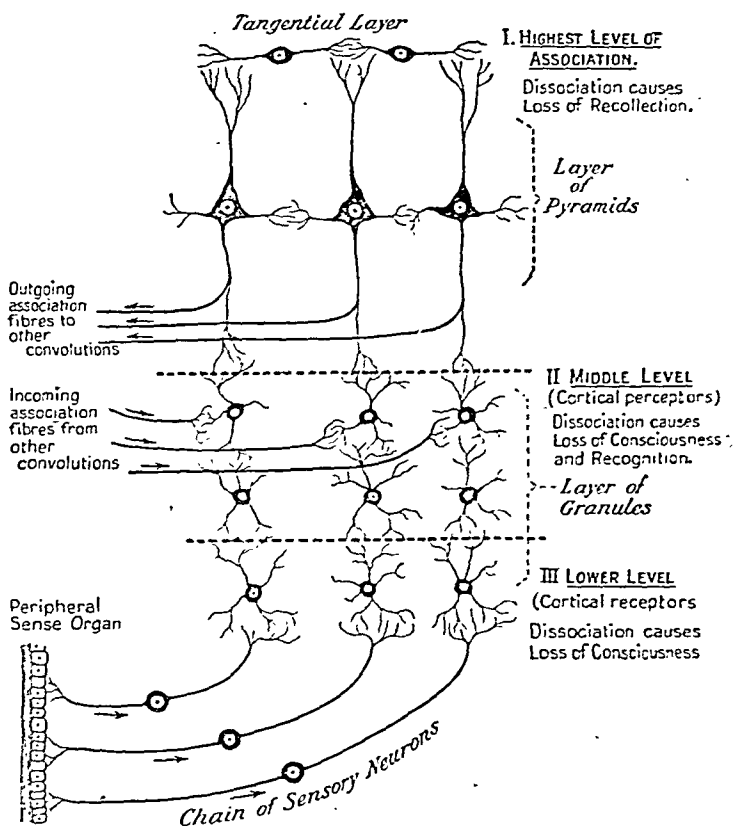


FIG. 227.—Diagram to illustrate levels of association. This figure if taken absolutely suggests that all three levels are in the same part of the cortex. This is not the case. Moreover, it is possible that the lower levels may be sub-cortical. (Mott.)

of consciousness. If temporary this is known as fainting. It becomes evident that strangulation or section of the carotid arteries in the neck is a much less painful form of death than commonly supposed. There is evidence that in right-handed persons consciousness may depend particularly on the left frontal lobe, for occlusion of the blood supply to this region is particularly effective in producing unconsciousness (Critchley).

3. A reduction of the fuel supply to the brain produces results similar to those of deficient oxygen supply since both allow the "cerebral fires" to go out. This occurs if there is insufficient

* The word "carotid" is derived from the Greek word *karos* meaning deep sleep.

glucose in the blood to be oxidised, as in hypoglycæmia from an excessive dose of insulin, when convulsions or unconsciousness may supervene.

4. Unconsciousness or coma also results from diseases in which **toxic products** are abnormally produced or are retained, as in diabetes mellitus or nephritis. The poisonous substances probably act directly on the cerebral cells.

Consciousness is associated with the activities of the nervous system to differing degrees, and it is possible to indicate this diagrammatically (fig. 227), although it must be understood that there is no hard and fast line between the different levels.

Sleep.

We are all familiar with sleep but its exact nature is not clearly understood.

The first two hours of sleep are always the most profound; later on, relatively weak stimuli will cause awakening. Of the parts of the central nervous system, the spinal cord is always less deeply affected than the brain, but even the brain is never entirely irresponsive, and unless slumber is very profound, dreams are the subjective result of external stimuli. Sensations of sound appear to be the last to disappear as sleep comes on, and the first to be realised on waking.

Changes which occur during Sleep.—During normal sleep there is a general reduction of sympathetic activity as indicated by constriction of the pupil, slowing of the heart, slight fall of blood-pressure, and an increase in the volume of the limbs. If the subject falls asleep on a special balance (Mosso), the head end is found to become appreciably lighter indicating that blood has been withdrawn from the brain. This is confirmed by the fact that if the brain of a man is observed during sleep, it is seen to retract slightly from the trephine opening in the skull. It may be noted, too, that a similar phenomenon is produced by narcotic drugs which produce sleep. The waves of the encephalogram (see below) are at first increased and then decreased as sleep deepens.

It is known, too, that conditions which reduce sympathetic activity favour sleep, namely warmth, comfort, and the reduction of sensory stimulation by quiet and darkness, while their absence prevents it.

How far the reduction of sympathetic action is the cause of, and how far the result of sleep is a difficult problem.

A further complication is the recognised fact that fatigue, especially of the muscles, provided it is not excessive, also promotes sleep. This may also tend to cause the accumulation of blood in the fatigued muscles, but it is possible that the chemical products

of fatigue may be sleep-promoting. Some investigators claimed to have isolated specific sleep-promoting substance. It used to be considered unlikely that such chemical substances are responsible because of the fact that the awakening from sleep may be a very rapid event. It is, as we shall see, just possible that the localised accumulation of a substance like acetyl-choline which, as we have seen, is very rapidly destroyed, may be responsible.

Howell among others believes cerebral anæmia to be the cause, and attributes the sleepiness that follows a heavy meal to the mechanical effect of a dilatation of the abdominal vessels in producing a diminished blood-flow through the brain; but the sleep that normally comes on at the end of the day he believes to be produced by cerebral anæmia following dilatation of the blood-vessels of the skin, such dilatation being due to vasomotor fatigue, but studies of experimental sleep suggest that the cerebral changes are the primary cause. There is also a fall of the blood calcium in normal sleep, and in that produced by sedatives and hypnotism.

Experimental Sleep.—Sleep may be produced experimentally in a number of ways, notably by depressing the sympathetic, *e.g.* by the injection of ergotamine into the third ventricle of the brain (Hess), or by stimulating the parasympathetic by raising the pressure in the carotid sinus by connecting it, when isolated from the circulation but with its nervous connections intact, to an external pressure system. This latter procedure, it should be noted, reduces the activity of the knee-jerk (Wright and Schweitzer) and causes muscular relaxation.

The injection of dilute calcium chloride into the third ventricle has also been found by Demole to produce sleep. This effect is antagonised by the injection of potassium chloride.

Hess, Professor of Physiology in Zurich, found that stimulation of the mid-brain by a slowly rising and falling current also caused sleep, and has suggested the existence of a sleep centre in the region of the floor of the third ventricle. He found that the injection of calcium chloride into the region of the tuber cinereum also produced a sleep reversible by potassium chloride. The view that the mid-brain is specially concerned in sleep is supported by the fact that detailed post-mortem study, by Economo, of sleepy sickness (encephalitis lethargica) shows evidence of the effects of an inflammation in this region. The disease is characterised by prolonged apparently normal sleep, from which, however, it is always possible to waken the patient.

Considerable attention has been given to the *inhibition theory* of Pavlov, who has been able to produce experimentally in dogs a condition resembling normal sleep. He considers that normal sleep and hypnotic sleep are much more closely related than

has been usually thought, and that both are due to the irradiation of inhibition. The subject has already been dealt with under "Conditioned Reflexes." This view makes it possible that the inhibitory process need not occupy the whole of the cortex at a given time, and thus gives interesting explanations regarding sleep-walking, dreams, persistence of the sense of time during sleep, etc. Incidentally, it suggests that the popular idea that certain individuals are at times only half-awake has some scientific justification!

It is not, however, agreed by psychologists that hypnotic and normal sleep are so alike as Pavlov claimed.

The view that sleep depends on the activity of a localised part of the brain is supported by Ranson, who produced sleep by section of the lateral hypothalamus in monkeys. This view does not contradict that of Pavlov but rather supports it, for we know that parasympathetic activity is very commonly conditioned. As examples we may take the secretion of saliva, vomiting, constriction of the bronchi in asthma, and erection of the penis. The exact relationship of this "sleep centre" to the sympathetic is unknown. In this connection it should be noted that sleep occurring naturally or produced by narcosis, provided the narcotic does not stimulate, is always associated with diminished sympathetic as distinct from parasympathetic action. The pupil is constricted, the heart slowed, and digestion continues.

The Cause of Sleep.—In conclusion, we say that sleep occurs when certain parts of the cerebrum are inhibited, but that the inhibition is facilitated by states which promote cerebral anæmia or a generalised reduction of sympathetic activity. From a practical point of view it should be remembered that states, *e.g.* sensory stimulation or cold which cause increased sympathetic activity, are liable to prevent sleep. Thus the hot water bottle is justified.

The Relation of the Action of Narcotics and Anæsthesia to Sleep.

Many attempts have been made to relate the action of drugs which produce unconsciousness to sleep. It is well recognised that the sleep produced by narcotics is restful and beneficial, but it may be that they facilitate or initiate normal sleep. This sometimes occurs during the induction of anæsthesia. It will be realised that a narcotic only differs from an anæsthetic by convention. With the anæsthetic the unconsciousness is deeper and more easily reversible.

There can be no doubt that, as shown by Demoor, little round swellings are produced on the dendrites by the action of

anæsthetics and narcotics and the Nissl bodies of nerve-cells are no longer so easily stained. Many have tried to prove that such drugs produce unconsciousness by reducing cerebral oxidations, but the evidence for this is, however, so very slight that it may be ignored (see Henderson, 1930, and Pask, 1941). Some anæsthetics may act by becoming dissolved in the fatty cell envelopes, and certainly the effect of the older anæsthetics was usually proportional to their fat solvency. This constituted the basis of the well-known Meyer-Overton hypothesis. Several of the newer anæsthetics and narcotics are, however, not specially fat soluble and it now seems more probable that they act on enzyme systems in the cells or, as suggested by Moore and Roaf, by making some unstable compound with the cell protein. It might be that the drugs interfere with humoral transmission between the neurones of the cerebrum. However such drugs act, it is evident that neither they nor sleep do the same permanent harm as does prolonged deprivation of oxygen.

The Effect of Loss of Sleep.—It should be recognised by the public that sleep is the period of anabolism, repair, and growth, and a large allowance is therefore necessary in growing children, who, amongst the lower classes, are often seriously harmed by insufficiency of sleep.

A thorough investigation of the effect of sleeplessness in adults was made on himself and his colleagues by Kleitman of Chicago; they voluntarily went without sleep for periods varying from 40 to 115 hours. They could easily remain awake when actively engaged, but became drowsy when sitting and fell asleep immediately on lying down or on complete muscular relaxation. It is remarkable how normal they remained otherwise; their blood, urine, etc., were examined, as was also the condition of their heart, respiration, blood-pressure, temperature, appetite, digestion, basal metabolism, and reflexes. Any departures from the normal, if present at all, were trivial; subjectively the feeling of sleepiness was alone marked; ability to do mental arithmetic was unimpaired. The most essential factor in causing sleep is muscular relaxation; this causes a loss of proprioceptive reflexes which in activity are always in action.

The effect of loss of sleep not exceeding one night has been shown experimentally to have a beneficial effect during the first half of the following day, but thereafter there is a fall in efficiency which, in spite of sleep, may not be fully recovered for three days.

Experimental studies show also that although during the first three hours sleep is at its deepest it is not so recuperative relatively as the later five hours of lighter sleep. It would seem then that the duration is more important than the depth of sleep.

The Electrical Reactions of the Cortex.

Modern methods of amplification by means of valves have made it possible to study the action potentials of the cortex which occur during activity. These may be recorded direct from the brain of a lightly anæsthetised animal or from the scalp of man. During sleep or deep anæsthesia there is almost complete "silence," but during consciousness or light anæsthesia various rhythmical changes in

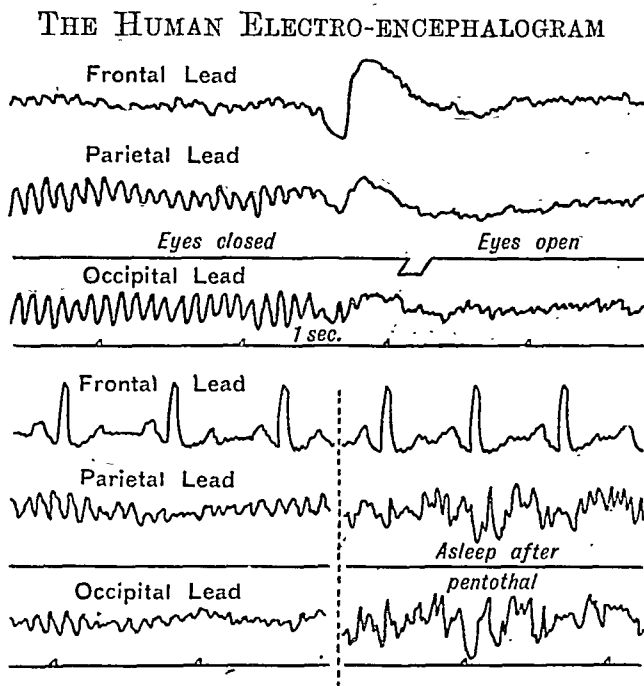


FIG. 228.—Encephalograms taken in subjects in different states. Note the special activity of the occipital cortex. (From records kindly supplied by Dr Dawson.)

potential are recorded—notably the Berger rhythm of the human electro-encephalogram. External stimuli sometimes synchronise independent normal rhythms. These electrical changes appear to be the result of groups of neurones in action—for it can readily be shown that the changes in special regions of the brain become increased or altered when corresponding sensory nerves are stimulated. For example, the occipital cortex becomes active when the eye is stimulated, but the inherent Berger rhythm is abolished. There seems little doubt afferent impulses are also concerned in the production of the electrical changes, for a section of the brain stem reduces the waves to those of deep sleep (Bremer, 1937), which is due to a slow synchronous discharge mainly of the occipital cortex. The alpha waves of Berger are reduced by mental activity or attention to any special stimulus. As a subject falls asleep the

waves are increased and in bursts, but later are reduced. Narcotics, anæsthetics, and hypnosis produced similar effects. Other waves and rhythms have also been described from other parts of the cortex. Dreams and epilepsy are associated with marked increases in the electrical changes. (Adrian, 1934, and subsequent papers in *Journal of Physiology*.)

It will, of course, be realised that these changes in electrical potential occur spontaneously, but fundamentally we may look upon them as produced similarly to those which may be recorded from the cortex when various sensory nerves are stimulated.

CHAPTER LI

VOLUNTARY MOVEMENT: CEREBELLUM, HYPOTHALAMUS, BASAL GANGLIA: SUMMARY

WHEN a decision is made to make a certain movement we may look upon the effective impulse as starting in the motor area of the cerebrum and passing down the **pyramidal tracts**.^{*} The pyramidal tracts arise in the larger pyramidal cells of the precentral gyrus. Thence the fibres converge, like the frame of a fan, through the corona

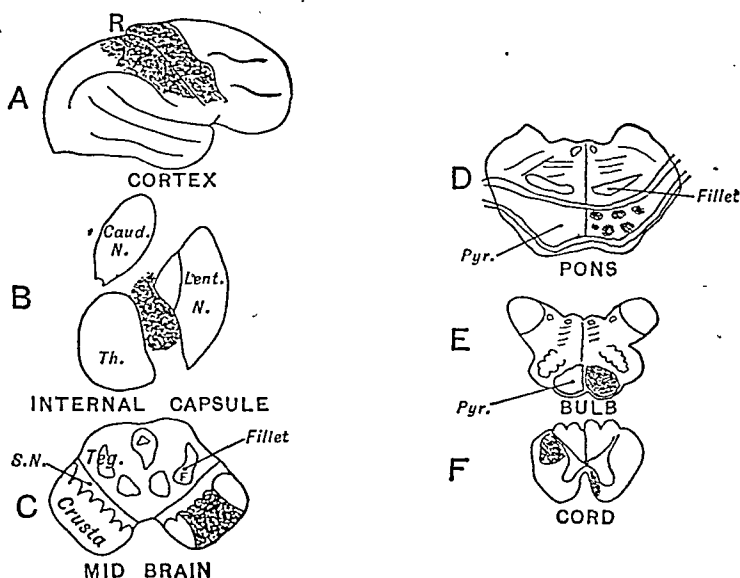


FIG. 229.—Degeneration after destruction of the Rolandic area of the right hemisphere. The black degenerated area shows the position of the pyramidal tracts throughout its course. (After Gowers.)

radiata to the internal capsule (fig. 229), where the fibres become bunched together between the lentiform nucleus externally and the thalamus and caudate nucleus on the inside (see also fig. 229, B). In horizontal section, the internal capsule appears bent. The pyramidal tracts lie at the bend and in the anterior two-thirds of the posterior limb, and from before backwards the fibres are arranged in order for the head, arm, trunk, legs. The posterior third of this limb is occupied by sensory fibres on their way from the thalamus to the cortex and by the final visual and auditory path. The anterior

^{*} These tracts consist of a million fibres and cannot arise slowly from the Betz cells of which there are only about 35,000.

limb of the capsule is occupied by fibres passing from the frontal lobe to the pons. The importance of this arrangement lies in the fact that a destruction of the fibres very readily occurs as a result of cerebral hæmorrhage in this region, and the localised paralysis which results depends on the actual damage done. These anatomical details have been ascertained by studying the detailed effects of destruction of the motor area. The effect of this is shown in fig. 229.

In the crus the fibres occupy the middle of the region in front of the substantia nigra (S.N.); in the pons the fibres are more scattered, but in the medulla they become again concentrated in the anterior aspect. In the lower part of the medulla most of the fibres cross to the opposite side at the decussation of the pyramids, the **crossed pyramidal tract** occupying the lateral column of the cord until it reaches its destination. In the lower part of the cord where the cerebellar tracts are small the pyramidal tracts extend to the lateral margin of the cord. The fibres of the tract end by arborising round internuncial cells in the region of the posterior horn (not the anterior), whence they are relayed to the anterior horn cells, whose axons pass out from the spinal cord to the muscles, etc. Some of the pyramidal fibres do not cross but remain as the **direct pyramidal tract** in the anterior aspect of the cord throughout, crossing, however, at intervals as far down as the lower thoracic region. Throughout its course in the brain the pyramidal tract gives off fibres *via* sensory cells (such as those in the substantia nigra) to the cranial nuclei.

The pyramidal tract is not found in all vertebrates below mammals, and its fibres are few in the lower mammals. In rodents they lie in the posterior columns. The direct pyramidal tract is found only in man and in the higher apes.

The **rubro-spinal tract** lies and functions in close association with the pyramidal tracts (see fig. 230) and, as we have seen, if it is cut, together with the pyramidal tracts, decerebrate rigidity results. It has its origin in the red nucleus, crosses in the mid-brain at the decussation of Florel and ends by synapsing in the lateral grey matter of the cord. Other descending tracts, the functions of which are unknown, are a few short tracts in the posterior columns, and the olivo-spinal tracts which may be concerned with equilibrium.

In clinical work the Betz cell and the pyramidal fibre are commonly known as the *upper motor neurone*, while the anterior horn cell with its axon is known as the *lower motor neurone*.

Destruction or damage to the pyramidal tracts results in paralysis of the particular part of the body supplied. If above the decussation of the pyramids in the medulla, as it commonly is in

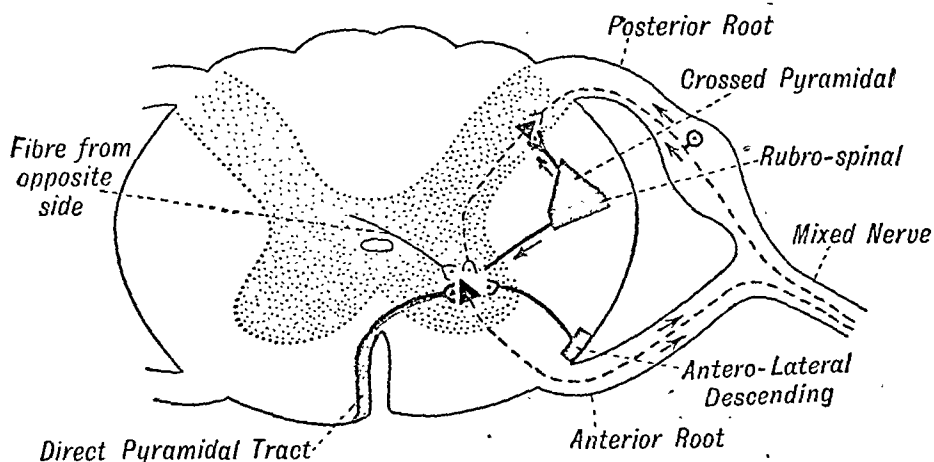
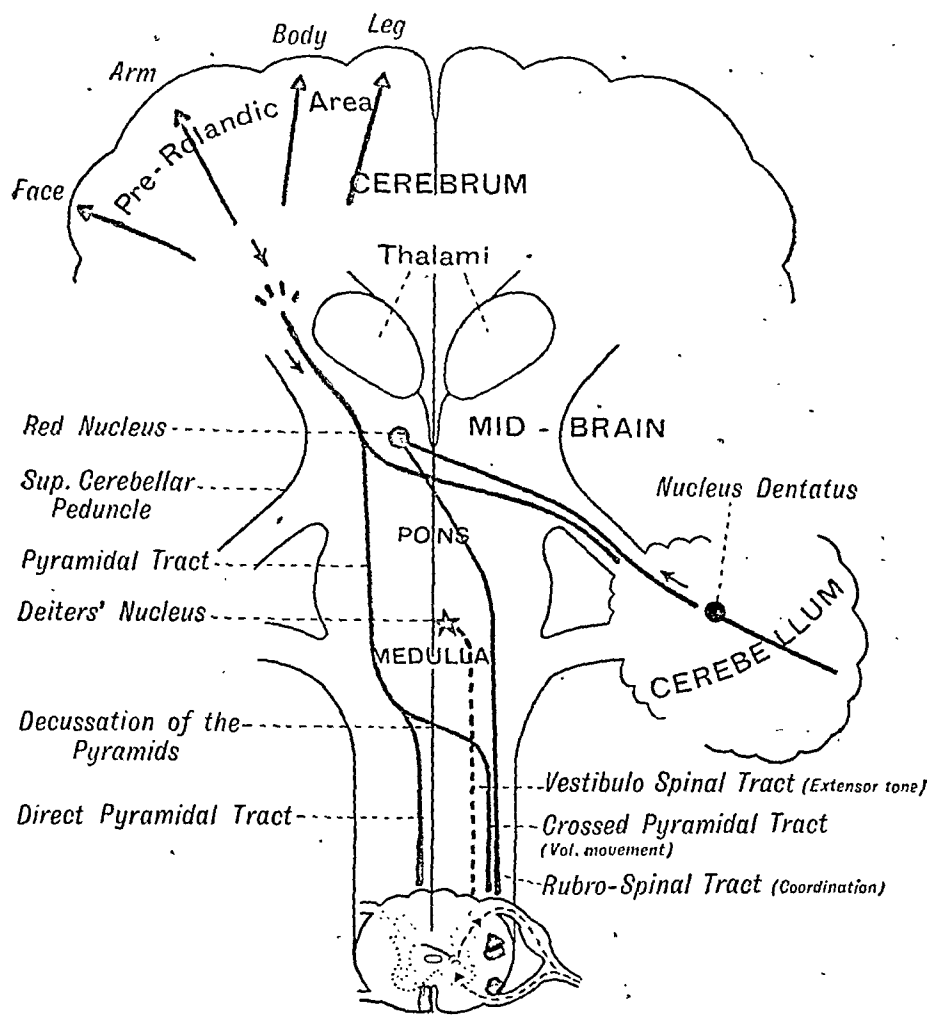


FIG. 230.—Main efferent paths in central nervous system. (From McDowall's *The Science of Signs and Symptoms*.)

cerebral hæmorrhage, the paralysis is on the opposite side of the body, although it may affect the muscles of the same side of the face.* If the motor area is damaged, as it may be at birth, paralysis of a single limb may occur. Even when both limbs of one side are affected (hemiplegia), the trunk, chest, and abdomen which are bilaterally innervated usually escape. The state of the muscles is somewhat reminiscent of decerebrate rigidity, the paralysed muscles have excessive tone (spasticity) and the deep reflexes of the part are increased.

Damage to the tracts in the spinal cord is less common. It may occur in injury and disease, *e.g.* tumour. In such conditions the interference with voluntary movement is, as a rule, accompanied by impairment of sensation also.

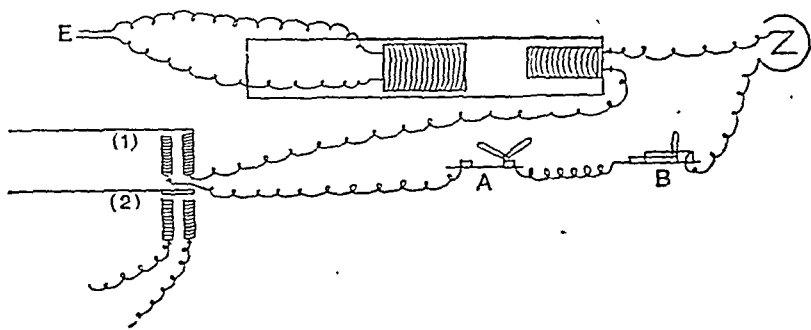


FIG. 231.—Diagram of apparatus for recording reaction time.

Useful voluntary activity does not, however, depend solely on the motor pathway. It depends also on sensation, as we have already seen on page 611, and it must be realised that diagrams such as that above are merely convenient ways of conveying a mental picture. All the evidence appears to indicate that when we move, say an arm, a shower of impulses is sent down the pyramidal tract to the anterior horn cells moving the essential muscles concerned, but that such contraction sets up at once groups of reflexes which modulate the activity of the muscles and the associated muscles. (See also p. 684.)

No doubt the cerebro-cerebellar connections, *via* the pontine nuclei, also play a part, but how they do so can only be conjecture. Possibly impulses pass down these pathways at the same time as they do the pyramidal tracts.

It is, however, to be understood that to consider the voluntary impulse as beginning in the motor area is merely convenient, as it

* This crossed paralysis involving the face on one side and the limbs on the other is characteristic of hæmorrhage into the pons. Lesions higher up, *e.g.* in the internal capsule, cause paralysis of the opposite face and limbs.

is the first point which we know of accurately. No doubt, impulses reach this area from the association areas and there is evidence that the frontal area may be specially concerned (Kinnier Wilson). The close relationship of the sensory to the motor area suggests that many of the stimuli come from the sensory area and there is little doubt that many of our so-called voluntary actions are more in response to direct sensory stimulation than at first sight appears. It is of interest also to observe that repetition of voluntary movement to a given stimulus (seen in taking reaction times) does cause an increased speed of response, while drugs, *e.g.* bromides, and diseases, *e.g.* myxedema, affect voluntary activity and reflexes.

Reaction Time in Man.—The term reaction time is applied to the time occupied in the central nervous system in that complex response to a pre-arranged stimulus in which the brain as well as the cord comes into play. It is sometimes called the *personal equation*. It may be most readily measured by the electrical

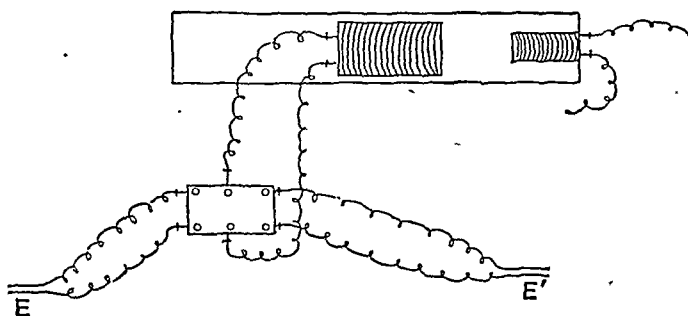


FIG. 232.—The dilemma.

method, and the diagram (fig. 231, p. 682) illustrates one of the numerous arrangements which have been proposed for the purpose.

In the primary circuit two keys (*A* and *B*) are included, and an electro-magnetic signal (1), arranged to write on a revolving cylinder (fast rate). A time marker or chronograph (2), marking 1-100ths of a second, is placed below this. The experiment is performed by two persons *C* and *D*. The key *A*, under the control of *C*, is opened. The key *B*, under the control of *D*, is closed. The electrodes *E* are applied to some part of *D*'s body. *C* closes *A*. The primary circuit is made, and the signal (1) moves. As soon as *D* feels the shock he opens *B*, the current is thus broken, and the lever of the signal returns to rest. The time between the two movements of the signal (1) is measured by means of the time-tracing written by chronograph (2). From this, the time occupied by transmission along the nerves has to be deducted, and the remainder is the *reaction time*. It usually varies from 0.15 to 0.2 second, but is increased in :—

The Dilemma.—The primary circuit is arranged as before. The wires from the secondary coil lead to the middle screws of a reverser without cross wires. To each pair of end screws, a pair of electrodes *E* and *E'* pass; these are applied to different parts of *D*'s body (fig. 232). It is arranged previously that *D* is to open *B*, when one part is stimulated, but not the other, *C* adjusting the reverser unknown to *D*. In these circumstances the reaction time is longer.

The reaction time in response to various kinds of stimuli, sound, light, pain, etc., varies a good deal; the condition of the subject of the experiment is also an important factor.

The Role of Afferent Impulses in Voluntary Movements.

Although, as we have said, voluntary movements are conveniently looked upon as commencing in the motor cortex of the cerebrum, afferent impulses play a large part in their initiation and accurate execution.

In the first instance, our decision to make any movement is almost invariably the result of an impulse from the external environment, which causes us to make the movement at a given time. Similarly, afferent impulses may cause us to move the part in a certain direction.

If the movement involves balance, all the impulses from the eyes, from the labyrinth, and from the muscles themselves determine the extent to which movement may be made and the necessary adjustment which is required to maintain equilibrium.

The impulses from the muscles themselves are of special importance in grading and co-ordinating. This is well seen when there is, as in tabes, disease of the posterior horns and posterior nerve roots. The patient is unable to judge exactly when his feet reach the ground in walking, his gait is therefore stamping and gives the name locomotor ataxia to the condition. All such impulses from the muscles are co-ordinated in the cerebellum, but how exactly they are linked to those of the pyramidal tracts is unknown.

Finally, afferent impulses may bring voluntary movement to an end as is well seen in the "Halt" of the drill instructor.

It is of interest to note in conclusion that when the sensory nerves are cut or damaged there is a disinclination to move the part. If the trigeminal nerve is cut (for neuralgia) the patient does not move his face unless specifically asked to do so. Similarly there is in tabes a lack of desire to move, and a similar state has been noticed in animals whose posterior roots are cut.

THE CEREBELLUM.

The cerebellum consists of a central lobe known as the vermis which connects two hemispheres, but unfortunately the usual anatomical descriptions bear no relation to function. Its outer cortex of grey matter is even more infolded than that of the cerebrum, and in the white matter of each hemisphere are situated masses of grey matter of which the most important are the dentate nuclei.

The grey matter is peculiar in possessing the cells of Purkinje, each of which has a bush-like dendron.

The **connections of the cerebellum** to the rest of the brain are by means of its **three peduncles** in which are the nerve-fibres which subserve its various functions, but the exact function of all these connections is by no means clear. (See fig. 233, p. 686.)

The *inferior peduncle* (I.P.), or restiform body, is composed of ascending fibres which pass into it—(1) from the cerebellar tracts of the same side, and (2) from the olivary nucleus of the opposite side; (3) from the nucleus gracilis and nucleus cuneatus of both sides (external and posterior arcuate fibres); (4) from the vestibular nerve, or from the nuclei in which it terminates in the pons.

The *middle peduncle* (M.P.) is formed of fibres which originate from the cells of the nucleus pontis: they pass from one side of the pons to the opposite cerebellar hemisphere.

In the higher mammals, which use their forelimbs freely, these connections are of special importance as the impulses from the motor area of the cerebrum pass through this way *via* the nuclei pontis.

The *superior peduncle* (S.P.) consists of (1) the axons of the cells of the nucleus dentatus and (2) fibres of the indirect spino-cerebellar tract. The axons arising from the nucleus dentatus decussate in the mid-brain with those of the opposite side, give off descending branches which terminate in the nucleus of Deiters, and furnish collaterals to the red nucleus and third nerve nucleus; they are then continued upwards to the optic thalamus. From the red nucleus the rubro-spinal tract arises, decussates with its fellow in the mid-brain, and descends to the spinal cord. From the optic thalamus a relay of fibres passes to the cerebral cortex.

Thus it will be seen that each half of the cerebellum receives impulses from the joints and muscles, mainly from the same side, *via* the spino-cerebellar tracts; from the labyrinth by means of the vestibular nerve of the same side; and from the cerebral cortex of the opposite side through the fronto-pontine tract and the nucleus pontis. Since the axons of the Purkinje cells of the cerebellar cortex end in the nucleus dentatus, the axons of which form a large part of the superior peduncle, one hemisphere of the cerebellum furnishes efferent impulses to the opposite cerebral hemisphere *via* the optic thalamus and to the same side of the spinal cord through the rubro-spinal tract; the impulses to the spinal cord must therefore cross the middle line twice. The cerebellum, through its superior peduncle, also gives impulses to the third nerve nucleus; the important part played by the cerebellum in the co-ordination of eye-movements is thus readily understood.

The **function of the cerebellum** was first pointed out by

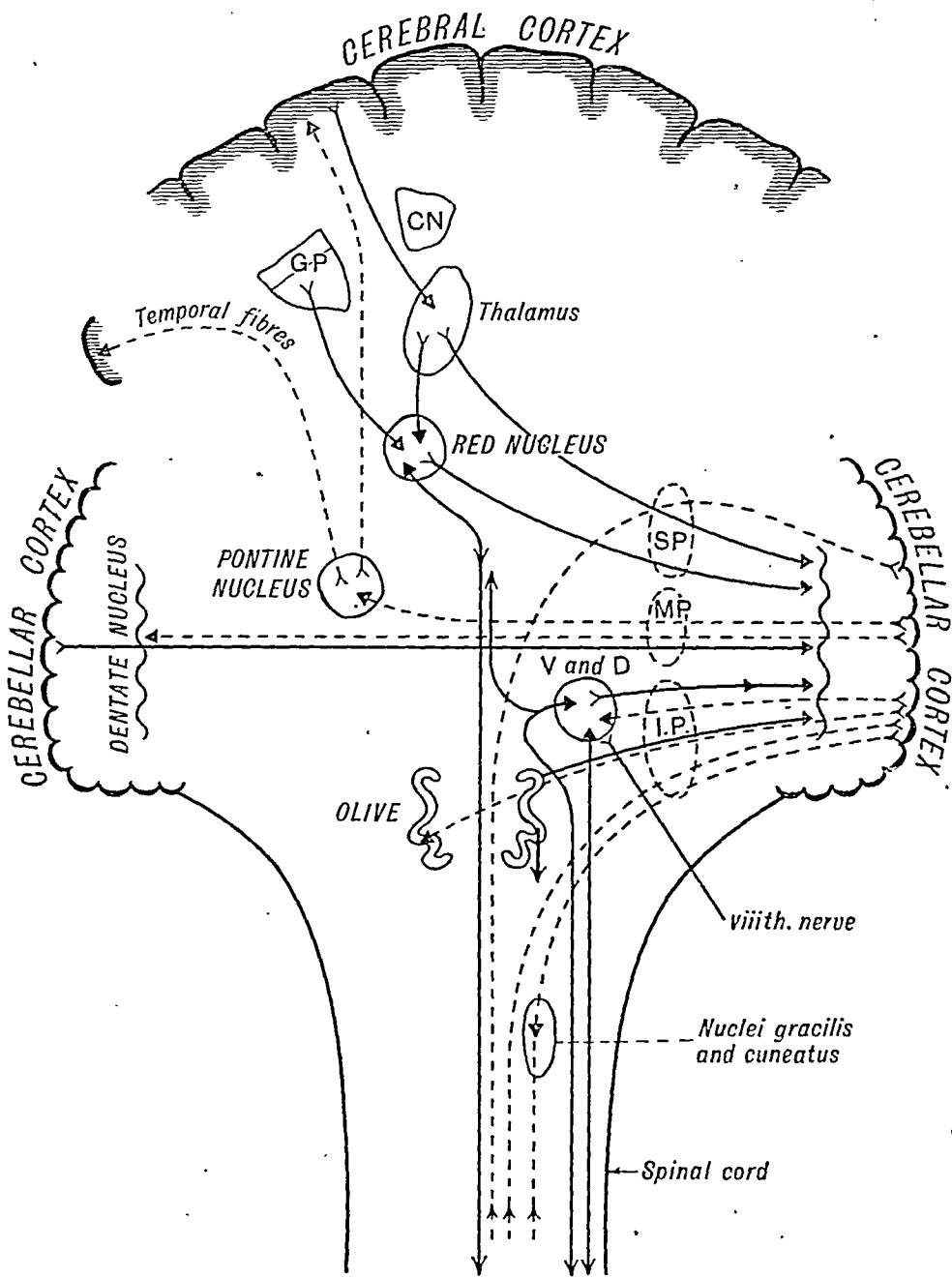


FIG 233.—The main connections of the cerebellum on one side. (After Heward Nicol.)

Flourens, who showed that the cerebellum is, as has been indicated already, the great centre for the co-ordination of muscular movement—that is, the harmonious adjustment of the working of the muscles; in doing so the cerebellum co-operates intimately with the postural mechanisms already described and with those responsible for voluntary movement.

Fulton describes it as a vast organ of the motor system lying in the downstream in the reflex arc from the cerebral cortex. There seems to be little doubt that it is particularly concerned with co-ordinated movements which have been acquired.

Its functions are suggested by its nervous connections (fig. 233) and by its development, a study of which has been made by anatomists, but have been largely confirmed and extended experimentally by extirpation experiments and by studying the electrical potential changes which are produced by various peripheral stimulation.

These functions fall into three main groups: (1) equilibration, (2) standing, (3) the co-ordination of muscular movement.

1. A study of its development in animals indicates that the organ is developed as an extension from the vestibular nucleus. Its earliest developed part of paleocerebellum (the flocculus and nodule) has therefore special connection with the vestibular part of the 8th nerve and is concerned with equilibrium. In fishes and birds this is well seen.

2. With the development of legs and the antigravity mechanisms the cerebellum becomes concerned with the impulses from muscles, especially from the limbs, and the spino-cerebellar tracts make their appearance and are associated with the development of a new part in the middle of the organ which go by different names, the paraflocculus P.F. with the pyramid. In this region representation of the various areas of the body is seen.

3. In the higher mammals in which free movement of the limbs, apart from standing and walking, becomes an established feature, the cerebellum takes on a still larger function in regard to co-ordination of muscular movement, and new afferent connections via the thalamus and efferent connections via the pontine nuclei between the cerebellum and the cerebrum become established. A new portion or neocerebellum (The Body) grows again into the middle of the existing cerebellum and becomes its largest part, but a study of the electrical changes of this region suggests that its function is largely associational. (See Localisation of Function below.)

The functions of the cerebellum have for the most part been

investigated by observing the effects of removal in animals and the effects of disease and removal for tumour in man.

As its development suggests the *effect of removal* in animals depends very much on the animal used and the use it makes of its muscles.

From the above we should expect that the lesion of the flocculo-nodular lobe should give rise to disturbances of equilibrium without necessarily any of limb reflexes or motor activity, whereas tumours of the body or the pathways to it will be expected to affect primarily co-ordination of muscular movement and produce tremor.

Lesions of the primitive flocculo-nodular lobe or tumours of the nodule give rise to a loss of equilibrium of the trunk, but there are no tremors and no disturbance of reflexes.

Flourens and many others used birds for their investigations because the organ in these animals is relatively large and accessible, and in these animals as in all others the disturbed condition of gait and the co-ordination necessary for flying contrasts forcibly with normal movements but sleepy state produced by removal of the cerebrum.

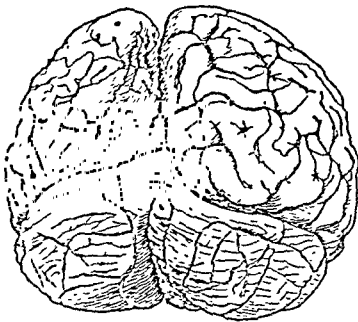


FIG. 234.—A photograph of a lunatic's brain (Fricke). One cerebral and the opposite cerebellar hemisphere are atrophied.

Removal of the most recently developed neocerebellum or body of the organ results in inco-ordination of the voluntary activities of mammals, and section of the superior peduncle which connects the organ to the cerebrum has a similar effect. (Larsell, 1937.) It has also long been known that faulty development of the cerebrum is associated with a similar failure to develop of the cerebellum (especially

the body) of the opposite side (see fig. 234). Removal of the anterior lobe connected with the spinal cord causes an increase of reflexes and of decerebrate rigidity (Sherrington), while stimulation has the opposite effect. No corresponding lesions have been described in man.

In **man** disease, such as tumour or abscess, of the cerebellum leads to the condition of cerebellar ataxia. This *ataxia* or disorderliness of walking is part of a general disturbance of co-ordination and is specially seen in lesions of the flocculo-nodular lobe but there is no tremor. There is general weakness (*asthenia*) and loss of tone (*atonia*) of the muscles concerned. The muscles, therefore, feel flabby and the limbs unduly loose and flail-like if moved. The individual is slow and clumsy and cannot bring his movements smoothly to an end. This

may be seen if the patient attempts to touch the nose; he not only has difficulty in reaching the nose, but he may strike the nose forcibly, while in attempting to make such an accurate movement the muscles act inco-ordinately instead of acting smoothly together (*asynergia*). There is also a coarse tremor of the hand and there may be nystagmus of the eyes (see below).

The weakness, if unilateral, tends to render him liable to fall

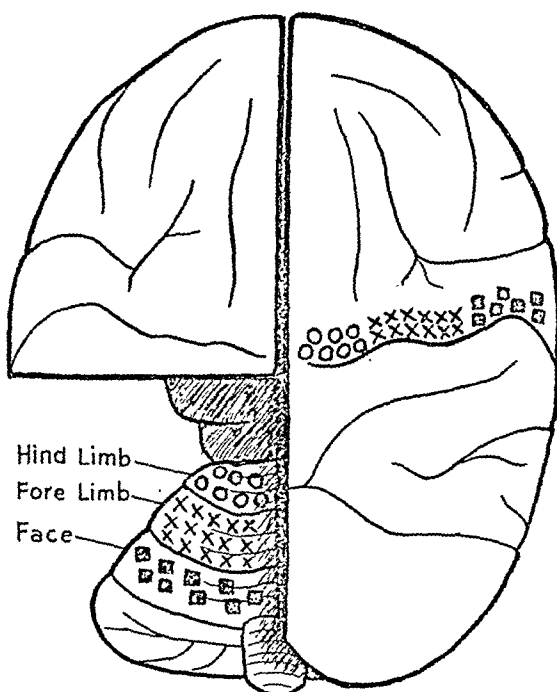


FIG. 235.—Diagram showing the points of receipt of afferent impulses on the surface of the cerebellum in the monkey and their relation to the cortex. (Adrian.)

to the *affected* side, since, as we have seen, the cerebellar tracts are uncrossed. The head is commonly rotated to the opposite side.

These facts are no doubt related to the observation that decerebrate rigidity is reduced by stimulation of the superior peduncle, of the anterior lobe or the roof nuclei, while lesions of these regions increase the rigidity, but no localised lesions of this kind have been described in man.

Speech may be similarly affected, being typically staccato in character or laboriously slow. There is also interference with the compensating movement of the eyes, the production of nystagmus (see p. 691) and deviation of the eyes. These disturbances result not only from disease of the cerebellum, but also when the paths to and

from the organ have been impaired, and may be considered to be due to an asynergy of the muscles concerned. The normal mechanism of the knee-jerk is disturbed. It is less sustained than normally, so that the leg appears to fall limply. The after-swing so produced has caused the term pendulum knee-jerk to be given to the response.

Localisation of Function.—It has now been shown, especially by Adrian and by Dow, that in the monkey afferent impulses are received on definite areas of the cerebellum, as we have seen occurs in the parietal region of the cerebrum (see fig. 235). Pressure on the pad of the foot and its dorsi flexions are particularly efficacious in setting up nerve impulses which can be traced electrically to the cerebellar cortex, but tactile stimuli and those set up by blowing on the hairs can be similarly traced. The area for the hind limbs is represented anteriorly in the lobus centralis, then the forelimb and the face, especially the vibrissa of the nose region, further back, the lobus simplex. In each case the pontine fibres are represented more laterally than the fibres from the spinal cord. It would seem that the vermis is concerned with the trunk movements. The bulk of the neocerebellum appears to be of the nature of an association or silent area. As in the case of the motor area of the cerebrum the afferent area for the forelimb is relatively large.

According to Bolk the upper surface is responsible for the thorax, neck, face, and arms, especially for adduction, abduction, and flexion, the lower surface controlling the lower part of the body, especially adduction and abduction of legs, but it now seems doubtful if this statement is generally applicable to all animals.

Recovery from Lesions.—The effects of removal of the cerebellum in animals is, however, not permanent; indeed, dogs, in which the cerebellum has been removed, recover their normal gait and do not appear otherwise abnormal. In man also, considerable degrees of recovery may be seen.

This recovery appears to be the result of other parts of the central nervous system, especially the cerebrum, taking over the functions of the cerebellum, since, if in recovered animals the cerebrum is now removed, the disturbance of gait returns.

These facts emphasise the intimate relationship between the cerebrum and the cerebellum. They suggest, indeed, that the cerebellum is not an essential organ in the sense that the movements cannot be carried out in its absence. It seems not unlikely, however, that by greatly facilitating co-ordination, movements may become very much easier, and that thereby the cerebrum is relieved of some of its duties. Complicated movements become as a result much more automatic than would otherwise be possible.

Compensating Movement of the Eyes.—Of considerable interest and importance is the movement of the eyes, which takes place automatically when the head is moved, so that they may remain fixed on an object. It may be observed in an animal whose cerebrum has been removed. If the head is moved up, the eyes move down, and *vice versa*. These eye movements depend on impulses from the labyrinth and from the muscles.

Similar movements may be observed in man: for instance, in an individual who attempts to look at passing objects from a rapidly moving train. The eyes appear to jump from one object to another. It would seem that this is a mechanism whereby during movement objects are retained in the retina sufficiently long to be appreciated. By its use if we pass through a station in an express train we see only certain objects distinctly but the rest are a blur. The jump is due to the cerebrum, but the lag behind which permits a series of objects to be focussed depends on cerebellar and brain-stem reflexes. The alternation of slow and fast movements of the eyes is known as **nystagmus**. A similar nystagmus, or difficulty in keeping the eyes fixed on an object held at the side of the head, is produced normally by heating or cooling the labyrinth, and is now a test for the efficiency of the latter in suspected disease. We have already remarked the interference with the normal position and movements of the eyes in cerebellar disease.

The Afferent Pathways of the Cerebellum.

The cerebellum receives impulses from the spinal cord by way of the **direct spino-cerebellar tract** (Flechsig) which arises from the cells of Clarke's column within the grey matter of the medial part of the base of the posterior horn. It does not degenerate if the posterior roots are cut. It lies in the dorso-lateral margin of the cord (see fig. 233) and passes to the cerebellum by the inferior peduncle.

Arising from Clarke's column also is the **indirect or ventral spino-cerebellar tract** of Gowers, which reaches the cerebellum by way of the superior peduncle, but some fibres go by the inferior peduncle. It will be observed that the cerebellar tracts *do not cross*.

THE EFFECT OF INJURY TO THE SPINAL CORD.

The study of paths makes it evident that an injury of, or a tumour pressing on, the spinal cord will affect its motor, sensory and reflex functions. On an accurate study of the changes brought about will depend the power of the surgeon to diagnose the exact position of the lesion and possibly to treat it. It is convenient to consider the effects of partial and complete section of the spinal cord.

Complete transverse section of the spinal cord may produce immediate death if the operation is performed sufficiently high in the cervical region, for the paralysed muscles will then include those of respiration. The spinal cells from which the phrenic and other respiratory nerves originate are then cut off from the respir-

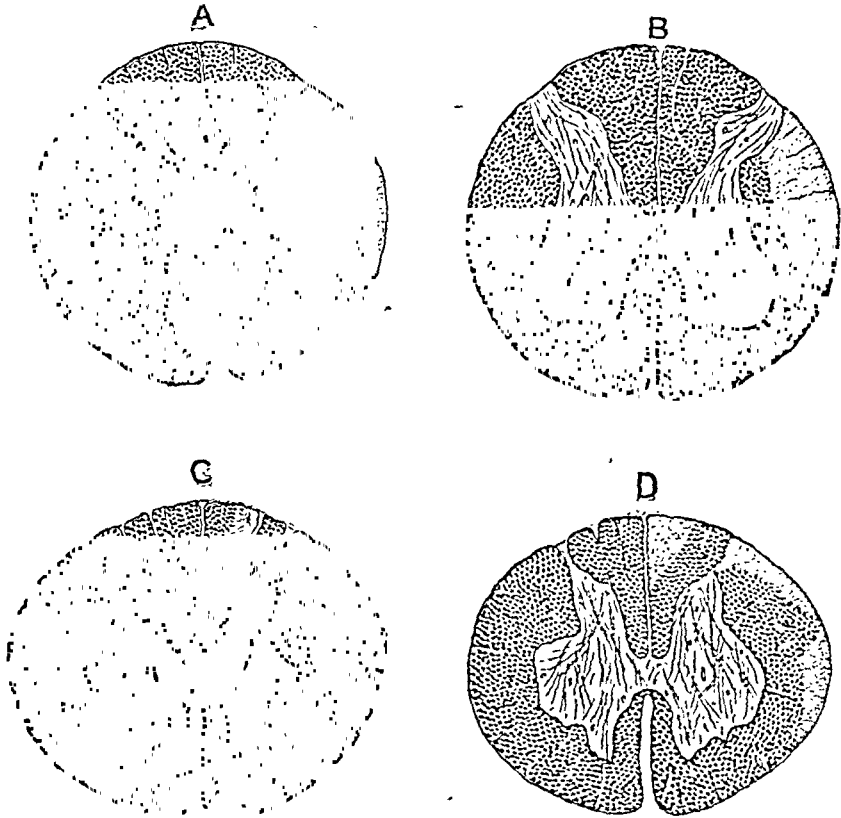


FIG. 236.—The above diagrams are reproductions of photo-micrographs from the spinal cord of a monkey, in which the operation of left hemisection had been performed some weeks previously (Mott). The sections were stained by Weigert's method, by which the grey matter is bleached, while the healthy white matter remains dark blue. The degenerated tracts are also bleached. A is a section of the cord in the thoracic region below the lesion; the crossed pyramidal tract is degenerated. B is a section lower down (in the lumbar enlargement); the degenerated pyramidal tract is now smaller. C is a section in the thoracic region some little distance above the lesion. The degenerated tracts seen are in the outer part of Goll's column, and the direct cerebellar tract. D is a section higher up in the cervical region; the degeneration in Goll's column now occupies a median position; the degenerations in the cerebellar tracts are also well shown. Notice that in all cases the main degenerated tracts are on the same side as the injury.

atory centre in the bulb above them, and the animal will die of asphyxia. One sees the same thing after severe injury to the upper cervical cord in man, as when he "breaks his neck."

If the injury is sufficiently low down and is not so abrupt that the patient or the animal does not die of shock, a series of typical changes are seen:—

1. Loss of motion of the parts supplied by the nerves below the section on both sides of the body.

2. Loss of sensation in the same regions.

3. Hyperæsthesia at the junction of the areas of normal and diminished or lost sensation.

4. There is an initial period of *spinal shock* during which all reflexes are absent, and specially important is loss of control of the urinary bladder which necessitates it being emptied by means of a catheter, a proceeding which is very liable to lead to fatal sepsis of the urinary tract. In man in about three weeks* there may be a considerable recovery of the reflexes, the typical flexor tone and exaggerated spinal reflexes, *i.e.* flexor withdrawal, appear (see p. 584). Reflex control of the bladder may return although voluntary control is permanently lost. Defæcation also takes place regularly.

5. There is loss of sympathetic control of the blood-vessels and viscera, resulting in generalised vasodilatation and a fall of blood-pressure, but these become re-established later. In animals an exaggerated peristalsis may be seen.

6. Degeneration, ascending and descending, on both sides of the cord.

Hemisection.—If the operation performed is not a complete cutting of the spinal cord transversely, but a cutting across of half the cord, it is termed hemisection. This leads to:—

1. Loss of voluntary control of the muscles of the same side below the level of the section.

2. Loss of sensation below the divided segment, approximately as follows: (a) Loss of joint and muscle sense, of sense of vibration, and of tactile discrimination, on the *same* side as the section; (b) Loss of the senses of pain, heat, and cold on the side *opposite* to the section. The reason for this peculiar distribution of sensory loss is the presence of an inferior and a superior sensory decussation; the former occurs within the cord as the decussation of the spino-thalamic fibres, the latter in the medulla as the decussation of the fillet.

In man these changes constitute the crossed paralyses of Brown-Séquard, who first described them.

3. Unilateral vasodilatation below the lesion and hyperæsthesia of the nearest healthy skin area above is also seen.

4. The tendon reflexes are at first absent but subsequently become exaggerated on the same side as the lesion as a result of the loss of the higher inhibition carried by the rubrospinal and pyramidal tracts.

5. Degeneration, ascending and descending, largely confined to the same side of the cord as the injury. The most important of these are shown in the preceding diagrams (fig. 236), the small text beneath which should be carefully studied.

* In cats the period of shock may be only a few minutes.

THE FUNCTIONS OF THE HYPOTHALAMIC REGION.

Of recent years a great deal of attention has been directed towards the region of the brain which lies just below the thalamus and above the mid-brain and the region adjacent to the floor of the third ventricle, and evidence appears to be accumulating that this region plays an important part in the elemental reactions of the body.

1. *Sex*.—It is suggested that the hypothalamus controls the action of the pituitary in regard to sex, but the evidence on the point is not convincing.

2. *Emotion*.—Particularly it is concerned with the reactions to emotion, which are only different from reflexes in that they are more complicated.

It has also been observed by Bard that removal of the frontal cortex in section of the fronto-hypothalamic tracts results in a remarkable condition of rage being produced, *e.g.* snarling, clawing, lashing of the tail, erection of the hairs, a rise of blood pressure and heart-rate, and dilatation of the pupil such as might be produced by the injection of adrenaline. When the hypothalamus is removed these symptoms disappear. It is possible to place electrodes in the hypothalamus of an otherwise intact animal, and when the animal has recovered from the anaesthetic, to stimulate the region. This also produces the state of rage.

The connections between the hypothalamus and the frontal lobe appear to be somehow concerned in the production of pathological mental depression in man, and patients suffering from this state cheer up when they are cut. Very rarely a liability to anger is observed after the operation. (M'Kissock.)

Normally, like the postural reflexes, they are more or less inhibited by the mediation of higher centres, and it is easy to see how anaesthetics like alcohol may, by paralysing the higher control centres, lead to loss of control of these lower activities. The liability of a partly drunk man to lose such control is well recognised.

3. *Body Temperature*.—There is no doubt also that the hypothalamus is concerned with the control of body temperature, which control is lost if this region is removed. The region specially concerned appears to be that of the tuber cinereum; damage to it may result in high body temperature. As might be expected, there are secondary changes in metabolic rate, sweating, and in water loss from the body.

4. *Sleep*.—This has already been discussed (see p. 673).

5. *Diuresis*.—Damage to the hypothalamic region is associated clinically with diabetes insipidus, with emaciation, and with Fröhlich's syndrome (see Pituitary).

6. Electrical stimulation of the posterior and lateral nuclei produces sympathetic effects like cardiac acceleration and inhibition of the gut, while stimulation of the mid-line nuclei causes opposite effects. Some have supposed that this indicates that the hypothalamus has some special relation to the autonomic nervous system, but many of these effects can equally well be produced by stimulation of the cerebral cortex (Fulton).

THE FUNCTION OF THE BASAL GANGLIA.

The difficulty of removing the basal ganglia such as the caudate or lenticular nuclei (see fig. 229), which are large masses of grey matter, has made it difficult to obtain information regarding their function. Evidence has, however, accumulated to indicate that disease of the lenticular nucleus produces motor disturbance of the face resembling laughter, increased reflexes and muscle tone, and in the condition of paralysis agitans or shaking palsy, which is characterised by great tremor of the hands or head, degeneration of the corpus striatum has been found post-mortem. It would seem, then, that the region of the basal ganglia probably controls some of the primitive movements.

A study has been made, especially by Fulton and his co-workers, of the connections of the basal ganglia. The evidence is very complete that they receive fibres and presumably impulses from the area in front of the motor area, especially an area (Brodmann's Area 6) in front of the arm area, the structure of which is the same as that of the motor area, but which has no Betz cells. From the basal ganglia fibres pass to the red nucleus and substantia nigra. Removal of the cortical area produces a typical spastic paralysis like a decerebrate rigidity. (Wilson.)

A SUMMARY OF THE FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM.

We are now in a position to get a complete picture of the functions of the nervous system as a whole. As we have said, throughout the animal kingdom it exists for the purpose of regulating the internal mechanism of the body and for adapting the activities of the body as a whole to its environment. As we ascend the zoological scale the animals become increasingly capable of adapting themselves to different kinds of environment, and this very largely because of their greater capability of locomotion, which in a sense may be considered the index of evolution, and it will be seen that

the nervous system is developed largely according to locomotory requirements.

A simple animal, such as a jelly-fish, which does not move much from place to place, has a nervous system capable only of protecting itself. It has a nerve net in which the essential elements of a simple reflex are found—that is, afferent fibres, central cells and efferent fibres.

Slightly higher animals, *e.g.* worms, which move but slightly more, have a central chain of ganglia; each ganglion looks after a segment, but there is co-operation between the ganglia for the protection of the whole. This is the basal function of the spinal cord and brain-stem of mammals.

As the animal becomes still more mobile it requires some arrangement for a greater supply of oxygen and fuel and there are developed the medulla and pons in which are situated the centres concerned with the control of the respiration and circulation. In addition, the facility of digestion is increased by the vagal activity controlling swallowing and secretion and alimentary movements. With this increased facility is necessitated a power of vomiting for protection against noxious substances swallowed.

With still greater mobility conferred by the acquisition of legs are developed the postural reflexes controlled from the upper part of the medulla to the mid-brain and greater co-ordination is provided by the development of the cerebellum in close association. In animals which move in three planes this organ is most pronounced.

Higher still in the hypothalamus we find centres which confer adaptation to variabilities of temperature and all the advantages of rapid chemical action which the warm-blooded animal possesses. This region may indeed be considered the head-region of the primitive system which has for its function the preservation of the individual and his species in so far that evidence is increasing that reproduction also is controlled from this region and the associated pituitary body which also controls growth. Here appear to be located the more violent reactions to environment.

Finally, we have the cerebrum which relates past to present experience and which permits of calculated adaptation to still more complicated environments and supplying by means of modern mechanical transport and communication still greater mobility of body and of thought.

Fig. 185 on p. 575 of the brains of different animals may now be restudied, and it will be seen how their structure is related to function.

As regards slower reactions the ductless glands furnish still further adaptations, the pituitary body, those of the species, that is, growth and reproduction, and the latter is the needs of the

species, not of the individual; the thyroid, those of the day, that is metabolic control; and the adrenals, those of the minute, the adaptation necessary for movements.

Thus we find as we ascend that the influence of the individual on the environment becomes increasingly greater. At one end of the scale there is the creature which dies when there is any appreciable environmental change; at the other, man, who, while capable of greater adaptation than the lower animals, is at the same time beyond them in being the creator and master of a large amount of his environment. (Ranson, 1937.)

CHAPTER LII

THE NUTRITION OF THE CENTRAL NERVOUS SYSTEM

THE local peculiarities of the circulation through the brain have already been described. Nowhere else in the body is the maintenance of an adequate blood-supply more important than in the central nervous system. Deprivation of the arterial blood-supply leads to irrecoverable death of the cortical nerve-cells in eight minutes; the cells of the spinal cord are somewhat more resistant (forty-five to sixty minutes); temporary interference with blood-supply to the cortex causes fainting, whilst anæmia of the bulb is soon fatal. The stage of depression or coma caused by anoxæmia (due to asphyxia or cerebral anæmia) is frequently preceded by a stage of excitation evidenced by convulsions. If the circulation is restored in time recovery of function occurs in the following order: (1) respiratory reflexes; (2) spinal reflexes; (3) cerebral function. For normal nervous activity to be maintained the blood must also have the correct chemical composition; for example, if the percentage of sugar falls below 0.04 per cent., coma ensues, preceded in animals by convulsions (see Hypoglycæmia, p. 477). A rise in intracranial pressure, by stimulating the vasomotor centre, evokes a marked rise of arterial blood-pressure. Since a raised intracranial pressure, due to a foreign body such as blood-clot, implies a corresponding diminution in the amount of blood in the cranial chamber, it is apparent that the rise in arterial pressure is in a sense protective, as it causes an increased blood-flow through the brain. The brain so adapts the circulation that it secures for itself the optimal blood-supply. In disease, however, the mechanism may no longer act beneficially; thus in the case of cerebral hæmorrhage the rise in the blood-pressure tends to cause greater bleeding.

The Cerebrospinal Fluid.

Whilst the exact rôle which the cerebrospinal fluid plays in connection with the nutrition of the nerve-tissue is uncertain, it is conveniently discussed here.

The cerebrospinal fluid is a watery fluid (specific gravity about 1005) which is found in the ventricles of the brain and in the cerebrospinal subarachnoid spaces. The fluid is formed by the

choroid plexuses which project into the ventricles; it escapes into the subarachnoid space through the foramina in the roof of the fourth ventricle (foramen of Magendie and foramina of Luschka). A choroid-plexus is a much-folded process of the pia mater, rich in blood-vessels; the ventricular aspect of the tufts is covered by ependyma modified to form a glandular epithelium, *i.e.*, the cells are not ciliated, are cuboidal, and often contain vacuoles. The proof that the plexus forms the fluid is threefold: (1) there are histological changes (swelling of the cells, etc.) after excessive formation of cerebrospinal fluid; (2) when the exit from a ventricle, *e.g.* the foramen of Monro, is blocked, the ventricle distends; if previously the choroid plexus of the ventricle is removed no distension occurs (Dandy and Blackfan); and (3) fluid has been seen exuding from the surface of an exposed plexus.

The total quantity of the cerebrospinal fluid in man is perhaps about 150 c.c. Normally it is being slowly formed and absorbed. The chief absorption occurs after the fluid has left the ventricles, *i.e.* while it is in the subarachnoid space, and takes place mainly into the blood-stream. A smaller fraction is absorbed into the perineural lymphatics of the cranial and spinal nerves. The exact path of absorption into the blood-vessels is, according to Weed, through the arachnoidal villi which project as blind processes of the arachnoid into the sinuses of the dura mater, especially the superior longitudinal. In later life the arachnoidal villi hypertrophy to form the Pacchionian bodies.

The cerebrospinal fluid exerts a certain pressure, about 120 mm. of water, so that when a cannula is inserted into the cisterna magna through the occipito-atlantal ligament or into the lumbar sac the fluid escapes freely at first, afterwards more slowly, till finally the flow practically ceases.

The fluid contains the crystalloid constituents of the blood-plasma; the chlorides are normally about 0.74 per cent. Glucose (0.09 per cent.), urea and creatinine are present in small amounts, together with a trace of protein (0.02 per cent.). The gases resemble those of lymph, but the proportion of carbon dioxide which is "fixed," *i.e.*, which cannot be removed by ebullition *in vacuo* without addition of acid, is greater than in lymph, which contains more protein.

The fluid obtained by cistern, or lumbar, puncture is said to be slightly richer in protein than that which fills the ventricles; for this and other reasons it is generally believed that there is added to the subarachnoid fluid a certain amount of fluid coming from the tissue of the brain and spinal cord *via* the perivascular spaces. The latter are inward prolongations of the subarachnoid space along the vessels which enter the brain at right angles, and communicate with the perineuronal spaces around the nerve-cells.

In health the cerebrospinal fluid contains but few cells (lymphocytes); the normal maximum rarely exceeds 5 per cubic millimetre. In meningitis the number of cells is enormously increased. The few

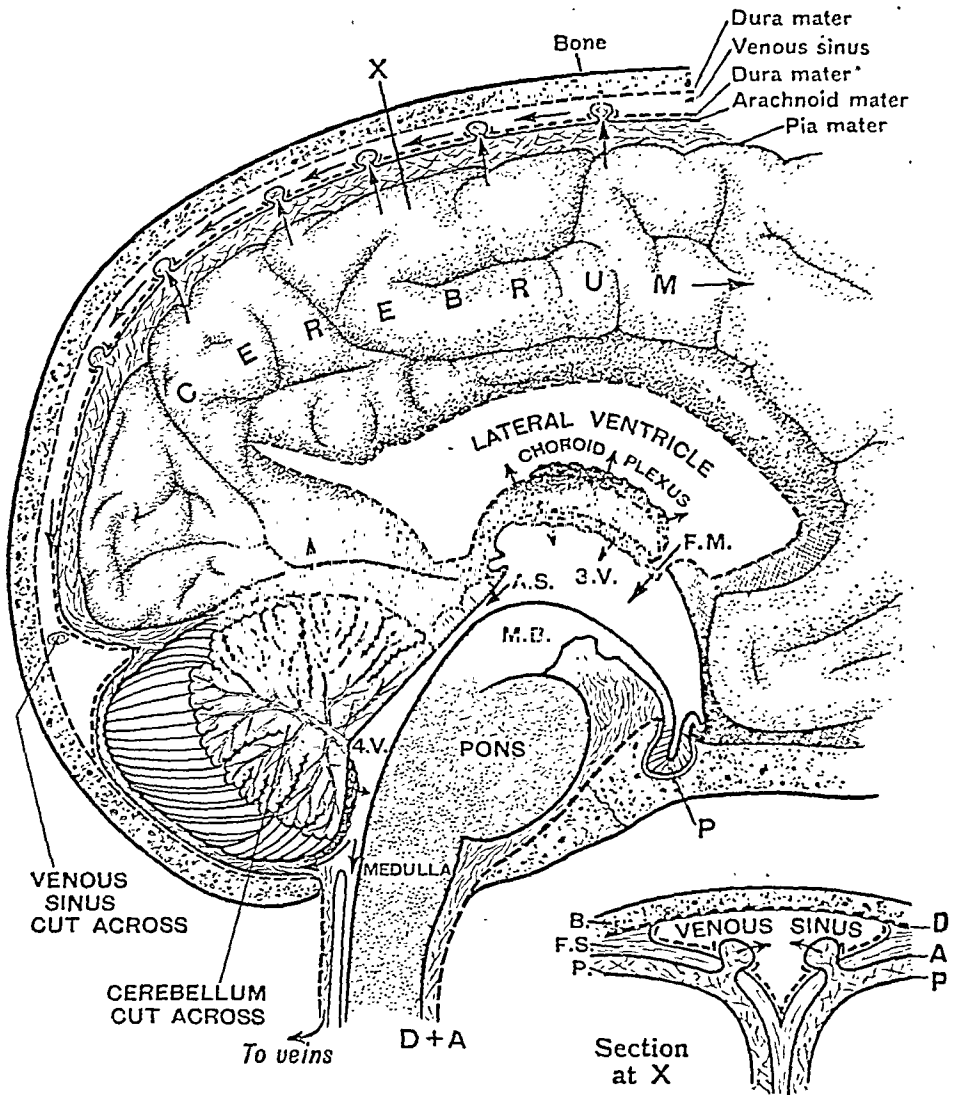


FIG. 237.—Diagram showing by means of arrows the origin and destination of the cerebrospinal fluid. The diagram is really of a medial section of the brain except that one lateral ventricle is shown.

cells normally present are supposed to be derived from the meningeal vessels.

The functions of this remarkable fluid are not by any means settled. It obviously affords mechanical protection to the central nervous system, and apparently receives such waste products from the central nervous system as are not absorbed by the blood-stream.

Moreover, the fluid can to a limited extent be displaced (*i.e.* absorbed) into the venous sinuses so as to accommodate an increased amount of blood in the cranial chamber.

Weed and McKibben showed that the intracranial pressure can be profoundly influenced by alterations in the osmotic pressure of the blood; the injection of hypotonic saline into a vein raises, while the administration of hypertonic saline lowers the pressure. The intravenous administration of hypertonic saline is frequently used therapeutically to lower excessive intracranial pressure.

The fluid can be regarded as an ideal Ringer-Locke solution in close relationship with the nerve-tissue. Dixon and Halliburton found that injection of extract of brain or chôroid plexus into a vein, or inhalation of carbon dioxide, caused an increased flow of cerebrospinal fluid; they suggested that the amount of fluid formed was perhaps controlled by the quantity of waste products produced by the brain. Pilocarpine is said to increase the formation of cerebrospinal fluid.

Substances introduced into the fluid readily pass into the blood; but the converse does not hold, for the choroid plexus permits the passage of certain substances only. It is noteworthy that alcohol readily enters the cerebrospinal fluid from the blood. (Weed, 1922 and 1933; Flexnor, 1934.)

CHAPTER LIII

SPEECH AND VOICE

Speech

THE discovery of a part of the cerebral cortex which was specially associated with speech was one of the first steps towards cerebral localisation. The French physician Broca came to the conclusion that patients who died from cerebral embolism and who had, previous to death, lost the power of speech, had commonly

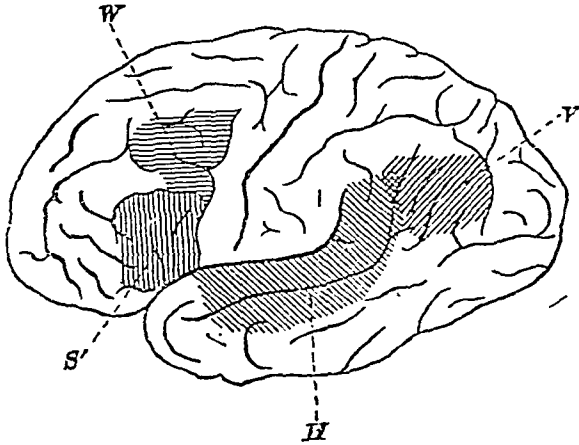


FIG. 233.—Lateral view of the left cerebral hemisphere of man (after Donaldson). V is the cortical area, damage to which produces "word blindness"; it is situated in the angular gyrus, and is called the *visual word centre*. H is the area in the superior temporal convolution, called the *auditory word centre*, damage to which produces "word deafness." S is Broca's convolution, damage to which produces loss of audible speech (motor aphasia); just behind is the motor area for the movements of the tongue, vocal cords, etc., concerned in speaking; Bastian termed it the *glosso-kinæsthetic area*. The area W, called by Bastian the *cheiro-kinæsthetic area*, is the corresponding region concerned in hand movements, damage to which abolishes the power of writing (agraphia).

damage in the region of the pars triangularis of the inferior frontal convolution. The most curious fact about this so-called speech centre is that it is situated only on the left side of the brain in right-handed persons.

Subsequently, Marie and Moutier pointed out that loss of speech may occur with lesions of other parts of the brain and that the loss may be confined to certain parts of speech; thus, the individual may be unable to read aloud, to write to dictation and

the like, without any other part of speech being seriously affected. Few will go so far as to suggest, as did Marie, that Broca's area has not a special relation to speech; indeed, there is overwhelming evidence that it has. Head went to the other extreme, and has almost denied that it is possible to differentiate *aphasia*, i.e. loss of speech, into isolated affections of speaking, writing, etc., due to destruction of visual, auditory, or motor areas.

The Formation of Speech.—Probably all these views may be reconciled when we consider how speech is evolved in the individual. Speech in its wide sense may be considered the mode of interchange of ideas between oneself and one's fellow-creatures. It may be looked upon as depending upon three distinct mechanisms.

(1) **A Receptor Mechanism** which may involve any sensation, although normally hearing and seeing are utilised. In close relationship to the cortical centre for these sensations are the association areas, in which memories of sensation appear to be stored. Thus, in the second and third temporal convolutions are stored the names of objects and these are lost if this region becomes the seat of disease, e.g. abscess secondary to inflammation of the middle ear.

(2) **Association Mechanism.**—Our knowledge of this mechanism is, as yet, quite crude, and we cannot relate its facts in any detail to anatomical areas, but from a study of disease a large amount of interesting material has been collected.

There is general agreement, however, that in right-handed persons the area concerned is on the *left* side of the brain, within a well-defined cortical region extending from the lower and posterior part of the frontal lobe, by the island of Reil, to the temporal and lower parietal and occipital region (Kinnier Wilson). Of this region, it is clear that the anterior part is concerned with expression, and the posterior part, or area of Wernicke, with reception.

To each sensation is attached a certain significance according to the circumstance in which it is experienced. If an idea has to be communicated, or a reply made, the impulse passes to that part of the association mechanism concerned with expression, where the proper means of expression is determined. Broca's area (as its histological structure suggests) may be considered an association area in close relation to the vocal effector mechanism.

(3) **An Effector Mechanism.**—The message is then conveyed to the appropriate part of the motor cortex concerned with the vocal organs, but it may be, according to circumstances, the area for hand movements or any other part. A nod of the head, or placing a finger to the mouth, may be even more significant than a spoken word. It is, then, fairly easy to understand why it is that certain parts of the general speech mechanisms may become impaired, leaving other

parts normal. Head does not consider that an aphasic individual is ever quite normal mentally, nor, indeed, can this be expected, unless the disease is limited to a small area of the motor cortex. When we learn to speak, we learn to think and to form ideas by a similar mechanism, and we know how impaired the general mentality of a deaf person may be, simply because he has not the normal facility of communicating with his fellows.

The effect of any given lesion on mentality will then depend on how the individual has acquired his knowledge. If, for example, there is a lesion of the association fibres connecting the visual association area to the motor area for the vocal organs, not only will the individual be word-blind, *i.e.* unable to read aloud, but probably other associations and ideas, which depend on knowledge acquired by reading, will be affected, although he may reply quite well to verbal questions, and knowledge acquired by hearing may be unaffected. (Wilson and Head.)

Voice Production.

The fundamental tones of the voice are produced by the current of expired air causing the vibration of the vocal cords, two bands

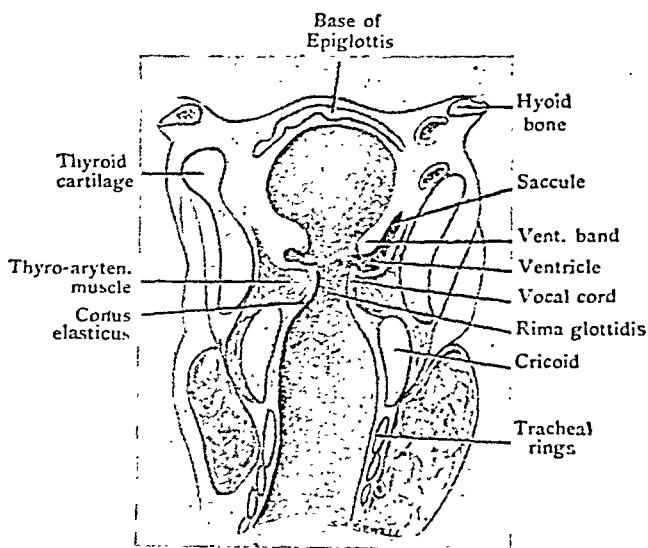


FIG. 239.—A vertical section through the larynx. It emphasises the fact that the vocal cords are not in reality cords but the apices of sharp folds. Note the valvular appearance of the laryngeal folds. The vocal cords prevent the entry of air into the chest, the ventricular bands hinder the exit of air. (V. E. Negus.)

contained in a cartilaginous box placed at the top of the windpipe or trachea. This box is called the *larynx*. The sounds produced here are modified by other parts such as the tongue, teeth, and lips, as will be explained later on.

For a detailed description of the larynx, reference should be made to a text-book of Anatomy. It is composed of the thyroid cartilage, the prominence in front of which constitutes Adam's apple, the cricoid cartilage and the two arytenoids, together with several minor cartilages. These are all held together and to the neighbouring structures by fibrous tissue and muscle.

Mucous Membrane.—The larynx is lined with a mucous membrane continuous with that of the trachea; this is covered with ciliated epithelium except over the vocal cords and epiglottis, where it is stratified. The vocal cords are bands of elastic tissue in this mucous membrane which run from before back. They are continuous below with the conus elasticus, and are attached as stated above. The chink between them is called the *rima glottidis* (see fig. 240). Two ridges of mucous membrane above and parallel to these are called the *false vocal cords*; between the true and false vocal cord on each side is a recess called the *ventricle*.

The laryngoscope is an instrument employed in investigating during life the condition of the pharynx, larynx, and trachea. It consists of a large concave mirror with perforated centre, and of a smaller mirror fixed in a long handle. The patient is placed in a chair, a good electric light is arranged on one side of, and a little above, his head. The operator fixes the large mirror to his head in such a manner that he looks through the central aperture with one eye. He then seats himself opposite the patient, and so alters the position of the mirror, which is for this purpose provided with a ball-and-socket joint, that a beam of light is reflected on the lips of the patient.

The patient is now directed to throw his head slightly backwards, and to open his mouth; the reflection from the mirror lights up the cavity of the mouth, and by a little alteration of the distance between the operator and the patient the point at which the greatest amount of light is reflected by the mirror—in other words, its focal length—is readily discovered. The small mirror fixed in the handle is then warmed, either by holding it over the lamp, or by putting it into a vessel of warm water; this is necessary to prevent the condensation of breath upon its surface. The degree of heat is regulated by applying the back of the mirror to the hand or cheek, when it should feel warm without being painful.

After these preliminaries the patient is directed to put out his tongue, which is held by the left hand gently but firmly against the lower teeth by means of a handkerchief. The warm mirror is passed to the back of the mouth, until it rests upon and slightly raises the base of the uvula; and at the same time the light is directed upon it: an inverted image of the larynx and trachea will be seen in the mirror. If the dorsum of the tongue is alone seen, the handle of the mirror must be slightly lowered until the larynx comes into view; care should be taken, however, not to move the mirror upon the uvula, as it excites retching. The observation should not be prolonged, but should rather be repeated at short intervals.

The structures seen will vary, according to the condition of the parts, during inspiration, expiration, phonation, etc.; they are (fig. 241) first, and apparently at the posterior part, the *base of the tongue*, immediately below which is the arcuate outline of the *epiglottis*, with its cushion or tubercle. Then are seen in the central line the *true vocal cords*, white and shining in their normal condition. The cords approximate (in the inverted image) posteriorly; between them is

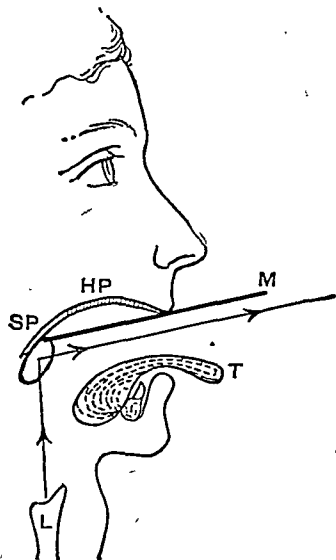


FIG. 240.—Diagram to illustrate the method of observing the larynx. The illumination may be from a forehead lamp or a lamp in the handle of the mirror. L, larynx; T, tongue; HP, hard palate; SP, soft palate. The arrows indicate a reflected beam of light from the larynx.

left a chink, narrow whilst a high note is being sung, wide during a deep inspiration. On each side of the true vocal cords, and on a higher level, are the pink *false vocal cords*. Still more externally than the false vocal cords is the *aryteno-epiglottidean fold*, in which are situated on each side two small elevations; of these the most external is the *cartilage of Wrisberg*, the inner is the *cartilage of Santorini*. The *rings of the trachea*, and even the bifurcation of the trachea itself, if the patient be directed to draw a deep breath, may be seen in the interval between the true vocal cords.

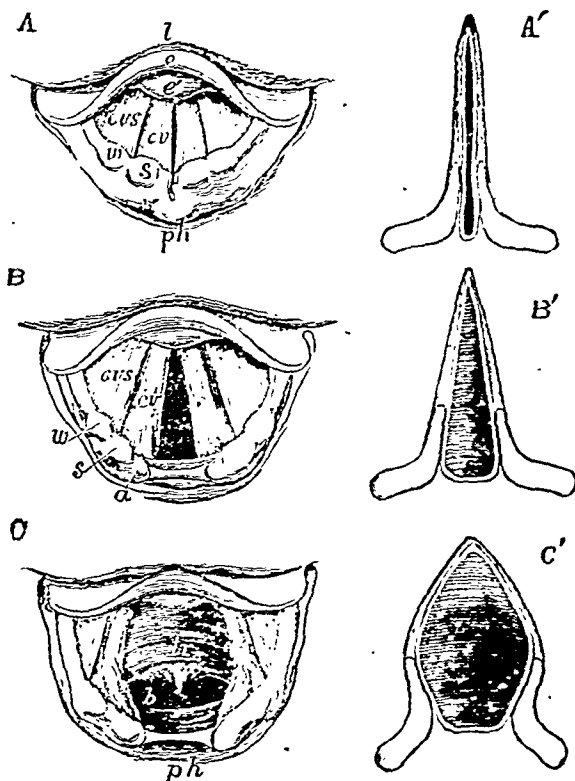


FIG. 241.—Three laryngoscopic views of the superior aperture of the larynx and surrounding parts. A, the glottis during the emission of a high note in singing; B, in easy and quiet inhalation of air; C, in the state of widest possible dilatation, as in inhaling a very deep breath. The diagrams A', B', C', show in horizontal sections of the glottis the position of the vocal cords and arytenoid cartilages in the three several states represented in the other figures. In all the figures so far as marked, the letters indicate the parts as follows, viz.: l, the base of the tongue; e, the upper free part of the epiglottis; e', the tubercle of the epiglottis; ph, part of the anterior wall of the pharynx behind the larynx; in the margin of the aryteno-epiglottidean fold, w, the swelling of the membrane caused by the cartilages of Wrisberg; s, that of the cartilages of Santorini; a, the tip or summit of the arytenoid cartilages; cv, the true vocal cords or lips of the rima glottidis; c v s, the superior or false vocal cords; between them the ventricle of the larynx; in C, tr is placed on the anterior wall of the receding trachea, and b indicates the commencement of the two bronchi beyond the bifurcation which may be brought into view in this state of extreme dilatation. (Quain, after Czermak.)

Movements of the Vocal Cords.

In Respiration.—The position of the vocal cords in ordinary tranquil breathing is so adapted by the muscles, that the opening of the glottis is wide and triangular (fig. 241, B). The glottis may remain unaltered during ordinary quiet breathing, though in

some people it becomes a little wider at each inspiration, and a little narrower at each expiration. In the cadaveric position the glottis has about half the width it has during ordinary breathing; during life, therefore, except during vocalisation, the abductors of the vocal cords (posterior crico-arytenoids) are in constant action. (F. Semon.) On making a rapid and deep inspiration the opening is widely dilated (fig. 241, c) and somewhat lozenge-shaped.

In Vocalisation.—At the moment of the emission of a note the chink is narrowed, the margins of the arytenoid cartilages being brought into contact, and the edges of the vocal cords approximated and made parallel (fig. 241, A); at the same time their elasticity is regulated by contraction of the thyro-arytenoid muscles. As the pitch of the note increases it is probable that the degree of contraction—and with it the elasticity—of the thyro-arytenoid muscles becomes greater, and the range of a voice depends, in the main, on the extent to which the degree of elasticity of the vocal cords can be thus altered. In the production of a high note the vocal cords are brought well within sight. In the utterance of low-pitched tones, on the other hand, the epiglottis appears to be brought over them, and the arytenoid cartilages look as if they were trying to hide themselves under it (fig. 242).

The approximation of the vocal cords also usually corresponds with the height of the note produced; but the width of the aperture has no influence on the pitch of the note, as long as the vocal cords have the same tension; only with a wide aperture the tone is more difficult to produce and is less perfect, the rushing of the air through the aperture being heard at the same time.

No true vocal sound is produced at the posterior part of the aperture of the glottis, namely, that which is formed by the space between the arytenoid cartilages (*pars intercartilaginea*).

The Voice.

The human musical instrument is often compared to a reed organ-pipe: certainly the notes produced by such pipes in the *vox humana* stop of organs is very like the human voice. Here there is not only the vibration of a column of air, but also of a reed, which corresponds to the vocal cords in the air-chamber composed of the trachea and the bronchial system beneath it. The pharynx, mouth,

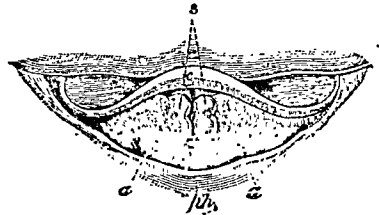


FIG. 242.—View of the upper part of the larynx as seen by means of the laryngoscope during the utterance of a bass note. *e*, Epiglottis; *s*, tubercles of the cartilages of Wrisberg; *a*, cartilages of Santorini; *z*, base of the tongue; *ph*, the posterior wall of the pharynx. (Czermak.)

and nasal cavities above the glottis are resonating cavities, which, by alterations in their shape and size, are able to pick out and emphasise certain component parts of the sounds produced in the larynx. The natural voice is often called the *chest voice*. The *falsetto voice* is differently explained by different observers; on laryngoscopic examination, the glottis is found to be blown open; it is probable that only the inner fibres of the thyro-arytenoid muscle are in contraction.

Musical sounds differ from one another in three ways:—

1. *In pitch*.—This depends on the rate of vibration; and in a string, the pitch increases with the tension, and diminishes with the length of the string. The vocal cords of a woman are shorter than those of a man, hence the higher pitched voice of women. The average length of the female cord is 11·5 millimetres; this can be stretched to 14; the male cord averages 15·5, and can be stretched to 19·5 millimetres.

2. *In loudness*.—This depends on the amplitude of the vibrations, and is increased by the force of the expiratory blast which sets the cords in motion.

3. *In "timbre"*.—This is the difference of character which distinguishes one voice, or one musical instrument, from another. It is due to admixture of the primary vibrations with secondary vibrations or overtones. The range of the voice is seldom, except in celebrated singers, more than two-and-a-half octaves, and for different voices this is in different parts of the musical scale.

Records may now be taken of the voice with accuracy as in the making of gramophone records, but the magnification required is such that they do not lend themselves readily to reproduction here.

Vocal Speech.

Speech is due to the modification produced in the fundamental laryngeal notes, by the resonating cavities above the vocal cords. By modifying the size and shape of the pharynx, mouth, and nose, certain overtones or harmonics are picked out and exaggerated: this gives us the vowel sounds; the consonants are produced by interruptions, more or less complete, of the outflowing air in different situations. When the larynx is passive, and the resonating cavities alone come into play, we get whispering.

The pitch of the Vowels has been estimated musically; *u* has the lowest pitch, then *o*, *a* (as in father), (*a* as in cane), *i*, and *e*. We may give a few examples of the shape of the resonating cavities in pronouncing vowel sounds, and producing their characteristic timbre: when sounding *a* (in father) the mouth has the shape of a funnel wide in front; the tongue lies on the floor of the mouth; the lips are wide open; the soft palate is moderately and the larynx slightly raised.

In pronouncing *u* (*oo*), the cavity of the mouth is shaped like a capacious flask

with a short narrow neck. The whole resonating cavity is then longest, the lips being protruded as far as possible; the larynx is depressed and the root of the tongue approaches the fauces.

In pronouncing *o*, the neck of the flask is shorter and wider, the lips being nearer the teeth; the larynx is slightly higher than in sounding *oo*.

In pronouncing *e*, the flask is a small one with a long narrow neck. The resonating chamber is then shortest as the larynx is raised as much as possible, and the mouth is bounded by the teeth, the lips being retracted; the approach of the tongue near the hard palate makes the long neck of the flask.

The Consonants are produced by a more or less complete closure of certain doors on the course of the outgoing blast. If the closure is complete, and the blast suddenly opens the door, the result is an *explosive*; if the door is partly closed, and the air rushes with a hiss through it, the result is an *aspirate*; if the door is nearly closed and its margins are thrown into vibration, the result is a *vibrative*; if the mouth is closed, and the sound has to find its way out through the nose, the result is a *resonant*.

These doors are four in number; Brücke called them the *articulation positions*. They are—

1. Between the lips.
2. Between the tongue and hard palate.
3. Between the tongue and soft palate.
4. Between the vocal cords.

The following table classifies the principal consonants according to this plan:—

Articulation position.	Explosives.	Aspirates.	Vibratives.	Resonants.
1	B, P.	F, V, W.	...	M.
2	T, D.	S, Z, L, Sch, Th.	R.	N.
3	K, G.	J, Ch.	Palatal R.	Ng.
4	...	H.	R of lower Saxon	...

The introduction of the phonograph has furnished us with an instrument which it is hoped in the future will enable us to state more accurately than has hitherto been possible the meaning of the changes in nature and intensity of the complex vibrations which constitute speech. (Fletcher, 1929; Curry, 1939.)

CHAPTER LIV

TASTE AND SMELL

Taste

THE crude anatomy of the tongue may be conveniently studied by means of a mirror in which the larger papilla may be seen at the back of the organ.

The tongue is a muscular organ covered by mucous membrane. This membrane resembles other mucous membranes in essential points, but contains *papillæ* peculiar to itself. The tongue is also beset with mucous glands and lymphoid nodules.

The lingual *papillæ* are thickly set over the anterior two-thirds of its upper surface, or *dorsum*, and give to it its characteristic roughness. Three principal varieties may be distinguished, namely, the (1) *circumvallate*, the (2) *fungiform*, and the (3) *conical and filiform* papillæ. They are all formed by a projection of the corium of the mucous membrane, covered by stratified epithelium; they contain special branches of blood-vessels and nerves. The corium in each kind is studded by microscopic papillæ.

(1) *Circumvallate*.—These large papillæ, eight or ten in number, are situate in a V-shaped line at the base of the tongue. They are circular elevations, from $\frac{1}{10}$ th to $\frac{1}{12}$ th of an inch wide (1 to 2 mm.), each with a slight central depression, and surrounded by a circular moat, at the outside of which again is a slightly elevated ring or rampart; their walls contain taste-buds. Into the moat that surrounds the central tower a few little glands (*glands of Ebner*) open. These glands form a thin, watery secretion.

(2) *Fungiform*.—The smaller fungiform papillæ are scattered chiefly over the sides and tip, and sparingly over the middle of the dorsum, of the tongue; their name is derived from their being shaped like a puff-ball fungus.

(3) *Conical and Filiform*.—These, which are the most abundant papillæ, are scattered over the whole upper surface of the tongue, but especially over the middle of the dorsum. They vary in shape, some being conical (simple or compound) and others filiform; they are covered by a thick layer of epithelium, which is either arranged

over them, in an imbricated manner, or is prolonged from their surface in the form of fine stiff projections in man. In carnivora they are developed into horny spines. These papillæ have a mechanical and tactile function, rather than one of taste; the latter sense is seated especially in the other two varieties of papillæ, the *circumvallate* and the *fungiform*.

In the circumvallate papillæ of the tongue of man peculiar structures known as *taste-buds* are found. They are of an oval shape, and consist of a number of closely packed, very narrow and fusiform, cells (*gustatory cells*). This central core of gustatory cells is enclosed in a single layer of broader fusiform cells (*encasing cells*). The gustatory cells terminate in fine stiff spikes which project on the free surface.

Taste-buds are also scattered over the posterior third of the tongue, the palate and the pharynx, as low as the posterior (laryngeal) surface of the epiglottis. The gustatory cells in the interior of the taste-buds are surrounded by arborisations of nerve-fibres.

The arrangement of papillæ, taste-buds, etc., varies a good deal in different animals. The *papilla foliata* of the rabbit's tongue consists of a number of closely packed papillæ very similar to the circumvallate papillæ of man; this forms a convenient source for the histological demonstration of taste-buds.

The middle of the dorsum of the tongue is but feebly endowed with the sense of taste; the tip and margins, and especially the posterior third of the dorsum (*i.e.*, in the region of the taste-buds), possess this faculty. The anterior part of the tongue is supplied by the *chorda tympani*, which runs with the lingual branch of the fifth nerve and the posterior third by the *glosso-pharyngeal* nerve. The lingual nerve is the nerve of general sensation of the tongue. The taste fibres from the anterior two-thirds of the tongue run in the lingual branch of the fifth nerve, leave it to enter the *chorda tympani*, and join the facial (seventh nerve). Their cells of origin lie in the geniculate ganglion of the facial. The central axons go in the *pars intermedia* to end in the upper end of the *nucleus solitarius*. The taste fibres from the posterior third of the tongue pass in the *glosso-pharyngeal* nerve; their parent cells are in the petrous ganglion and their central axons constitute the main part of the *fasciculus solitarius*. The taste nuclei in the brain stem are interconnected, and relay fibres eventually reach the cerebrum in the region of the *uncus*.

Tastes may be classified into—

- | | |
|------------------|------------|
| 1. Sweet. | 2. Bitter. |
| 3. Acid or Sour. | 4. Salt. |

Whether alkaline and metallic tastes are elementary is as yet undecided. All the above affect to a varying extent the nerves of

tactile sense as well as those of touch proper, sweet having the least, acids the most marked action upon the latter. Sweet tastes are best appreciated by the tip, acid at the side, and bitter tastes at the back of the tongue.

The substance to be tasted must be dissolved; here there is a striking contrast to the sense of smell; flavours are really odours. In testing the sense of taste in a patient, the tongue should be protruded, and drops of the substance to be tasted applied with a camel's hair brush to the different parts; the subject of the experiment must signify his sensations by signs, for if he withdraws the tongue to speak, the material gets widely spread. The more concentrated the solution, and the larger the surface acted on the more intense is the taste; some tastes are perceived more rapidly than others, saline tastes the most rapidly of all. The best temperature of the substance to be tasted is from 10° to 35° C. Very high or very low temperatures deaden the sense.

Individual papillæ, when thus treated with various solutions, show great diversity: from some only one or two tastes can be evoked, from others all four. The papillæ may also be stimulated electrically.

Cocaine and gymnemic acid, prepared from the leaves of the plant *Gymnema Sylvestre*, act deleteriously, chiefly on the bitter and sweet tastes; cocaine abolishes especially the bitter, gymnemic acid especially the sweet, leaving the salt and acid tastes almost untouched.

It will thus be seen that there are many facts pointing to the conclusion that the varieties of gustatory, like those of cutaneous sensation, are due to the stimulation of different end-organs.

When diluted sweet and salt solutions are simultaneously applied to the tongue, they tend to neutralise one another, but a true indifferent point is difficult or impossible to reach. Sweet and bitter, sweet and acid liquids are antagonistic to a similar but less perfect extent. Contrast-effects of one taste upon another are matters of common observation, but can be experimentally investigated only with difficulty.

Smell.

The entrance to the nasal cavity is lined with a mucous membrane closely resembling the skin. The greater part of the rest of the cavity is lined with ciliated epithelium; the corium is thick and contains numerous mucous glands. The olfactory region in man is limited to a portion of the membrane covering the upper turbinal bone, and the adjacent portion of the nasal septum; it is only 245 square millimetres in area. The cells in the epithelium here are of several kinds:—first, columnar cells not ciliated (fig. 243A), with the broad end at the surface, and below tapering into

an irregular branched process or processes, the terminations of which pass into the next layer: the second kind of cell (fig. 243) consists of a small cell body with large spherical nucleus, situated between the ends of the first kind of cell, and sending upwards a process to the surface between the cells of the first kind, and from the other pole of the nucleus a process towards the corium. The latter process is very delicate, and may be varicose. The upper process is prolonged beyond the surface, where it becomes stiff, and in some animals, such as the frog, is provided with hairs. These cells, which are called *olfactorial cells*, are numerous, and the nuclei of the cells not being on the same level, a comparatively thick nuclear layer is the

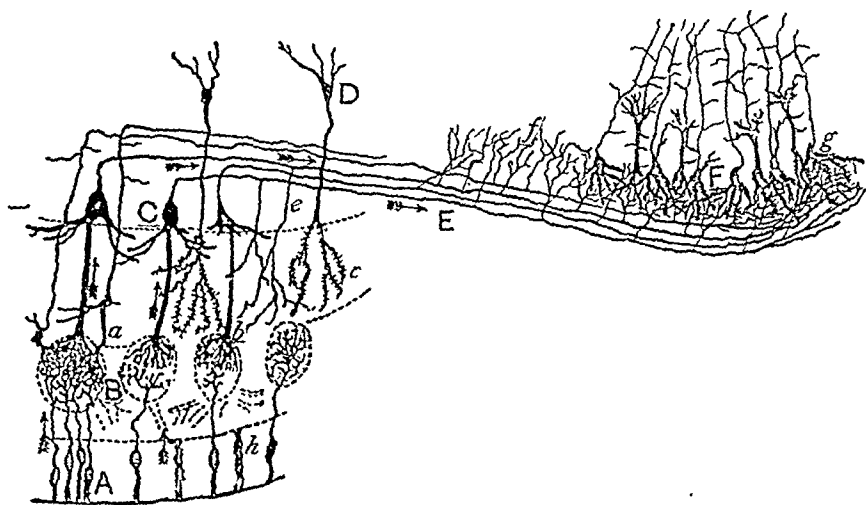


FIG. 243.—Nervous mechanism of the olfactory apparatus. A, bipolar cells of the olfactory apparatus (Max Schultze's olfactorial cells); B, olfactory glomeruli; C, mitral cells; D, granule of white matter; E, external root of the olfactory tract; F, grey matter of the sphenoidal region of the brain; a, small cell of the mitral layer; b, basket of a glomerulus; c, spiny basket of a granule; e, collateral of the axis-cylinder process of a mitral cell; f, collaterals terminating in the outer fibre layer of the olfactory cortex (archipallium); g, superficial triangular cells of the cortex; h, supporting epithelium cells of the olfactory mucous membrane. (Ramón y Cajal.)

result. They are in reality bipolar nerve-cells. In the corium are a number of serous glands called Bowman's glands. They open upon the surface by fine ducts passing up between the epithelium cells.

The distribution of the olfactory nerves which penetrate the cribriform plate of the ethmoid bone and pass from this region to the olfactory bulb is shown in fig. 243. The nerve-fibres are the central axons of the bipolar nerve-cells we have termed olfactorial; the columnar cells between these act as supports to them.

The *olfactory bulb* has a more complicated structure; above there is first a continuation of the olfactory tract (white fibres enclosing neuroglia); below this four layers are distinguishable; they are shown in the accompanying diagram from Ramón y Cajal's work, the histological method used being Golgi's.

(1) A layer of white fibres containing numerous small cells, or "*granules*" (D).

(2) A layer of large nerve-cells called "*mitral cells*" (C), with smaller cells (a) mixed with them. The axons of the mitral cells pass up into the layer above and eventually become fibres of the olfactory tract E, which passes to the grey matter of the base of the brain F. They give off numerous collaterals on the way (e, f).

(3) The layer of *olfactory glomeruli* (B). Each glomerulus is a basket-work of fibrils derived on the one hand from the terminal arborisations of the mitral cells, and on the other from similar arborisations of the non-medullated fibres which form the next layer.

(4) *The layer of olfactory nerve-fibres*.—These are non-medullated; they continue upwards the *bipolar olfactory cells*, which are placed among the epithelial cells of the mucous membrane.

The fibres from the olfactory mucous membrane pass through the cribriform plate at the base of the skull to end round cells in the olfactory bulb, which in animals which depend on smell is very well developed. A new relay arises here constituting the olfactory tract.

The olfactory tract is an outgrowth of the brain, which is originally hollow, and remains so in many animals; in man the cavity is obliterated, and the centre is occupied by neuroglia: outside this the white fibres lie, and a thin superficial layer of neuroglia covers these. The two white "*roots*" of the olfactory tract have been traced to the uncinate gyrus and hippocampal regions of the same side of the brain, which is the portion experimentally found to be associated with the reception of olfactory impulses. From the cells of the grey matter here fibres pass by a complex path to the corresponding regions of the opposite side. There is also a communication *via* the fornix and corpora mammillaria with the thalamus and tegmentum of the mid-brain.

Animals may be divided into three classes:—those which, like the porpoise, have no sense of smell (*anosmatic*); those which possess it in comparatively feeble degree (man, most primates, monotremes, and some cetacea); these are called *microsmatic*. In man the thickness of the olfactory membrane is only 0.06 mm. Most mammals are in contradistinction *macrosmatic*, the thickness of the membrane being 0.1 mm. or more, and its area larger.

The mucous membrane must be neither too dry nor too moist; if we have a cold we are unable to smell odours or appreciate flavours (which are really odours). When liquids are poured into the nose, their smell is imperceptible, as they damage the olfactory epithelium, owing to the difference of osmotic pressure. But even if a "*normal*" saline solution of an odorous substance is substituted, the sense of

smell is still lost so long as air-bubbles are carefully excluded from the nasal cavity. It is therefore necessary that odorous substances should be in a gaseous state in order to act upon the olfactory nerve-endings; they are normally conveyed to the olfactory surface by the air currents passing through the nose.

Generally, the odours of homologous series of compounds increase in intensity with increase of molecular weight, but bodies of very low molecular weight are odourless, while vapours of very high molecular weight, which escape and diffuse slowly, have little or no smell. A slight change in chemical constitution may produce marked alteration in the character of the odour of a substance; certain modes of atomic grouping within the molecule appear to be more odoriferous than others. Attempts have been made to discover the elementary sensations of smell, but hitherto with scant success. Many odours have unquestionably a complex physiological effect. For example, when nitrobenzol is held before the nose, it yields first the smell of heliotrope, next the smell of bitter almonds, and finally the smell of benzene; just as if different end-organs became successively fatigued. Some substances have a very different smell according to their concentration. Chemical dissociation, too, unquestionably plays a prominent part.

Nevertheless, there are certain observations which indicate the existence of primary sensations of smell. First, some persons are congenitally insensible to one or more odours, but yet smell others quite normally. Hydrocyanic acid, mignonette, violet, vanilla, benzoin, are substances which appear to certain people to have no smell. Secondly, some odorous bodies, when simultaneously given, antagonise one another; others produce a mixed smell. Thirdly, fatigue of the epithelium with one odour will modify or abolish the effect of some smells, but will leave that of others untouched.

The delicacy of the sense of smell is most remarkable even in man. Valentin calculated that even $\frac{3}{100,000,000}$ of a grain of musk can be distinctly smelt. Solutions of camphor afford a good means of testing olfactory acuity. Two tubes of camphor solution are presented to the subject along with two tubes of water, and the former pair is replaced with weaker and weaker solutions until it is indistinguishable from the tubes containing water. Pungent substances, such as ammonia, are unsuited for olfactometrical experiment. They stimulate the endings of the fifth (trigeminal) as well as those of the olfactory nerve. (Parker, 1922.)

CHAPTER LV

HEARING

Anatomy of the Ear

THE Organ of Hearing is divided into three parts, (1) the external, (2) the middle, and (3) the internal ear.

External Ear.—The external ear consists of the *pinna* and the *external auditory meatus*. The central hollow of the former is named the *concha*. The auditory meatus, with a slight arch directed upwards, passes inwards and a little forwards to the *membrana tympani*, to which it thus serves to convey the vibrating air.

Middle Ear or Tympanum.—The middle ear, or tympanum or drum (fig. 244), is separated by the *membrana tympani* from the external auditory meatus. It is a cavity, the only opening of which to the external air is through the Eustachian tube (E.T., fig. 244). The walls of the tympanum are osseous, except where apertures in them are closed with membrane, as at the *fenestra rotunda* and *fenestra ovalis*, and at the outer part where the bone is replaced by the *membrana tympani*. Its cavity is lined with mucous membrane, which is continuous through the Eustachian tube with that of the pharynx. A chain of small bones extends from the *membrana tympani* to the *fenestra ovalis*.

The *membrana tympani* is placed in a slanting direction at the bottom of the external auditory canal, and consists of fibres, some running radially, some circularly; its margin is set in a bony groove; its outer surface is covered with a continuation of the cutaneous lining of the auditory canal, its inner surface with the mucous membrane of the tympanum.

The *ossicles* are three in number; named malleus, incus, and stapes. The malleus, or hammer-bone, has a long slightly-curved process, called its handle, which is inserted vertically between the layers of the *membrana tympani*. The head of the malleus is irregularly rounded; its neck, or the line of boundary between the head and the handle, supports two processes: a *short* conical one, and a *slender* one (*processus gracilis*), which extends forwards, and is attached to the wall of the cavity at the Glaserian fissure. The *incus*, or anvil-bone, shaped like a bicuspid molar tooth, is articulated

by its broader part, corresponding with the surface of the crown of the tooth, to the malleus. Of its two processes, one, directed backwards, has a free end attached by a ligament to the wall; the other, curved downwards, longer and more pointed, articulates with the *stapes*, a little bone shaped like a stirrup, of which the base fits into the membrane of the fenestra ovalis.

The *muscles of the tympanum* are two in number. The *tensor tympani* arises from the cartilaginous end of the Eustachian tube

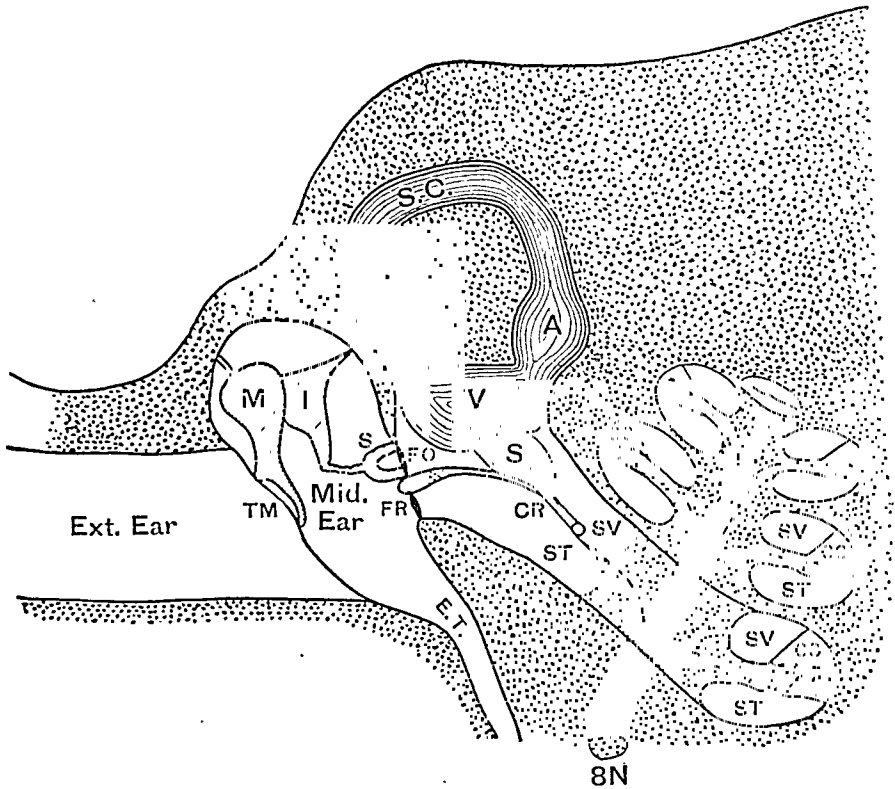


FIG. 244.—Diagram of ear. TM, tympanic membrane; M, malleus; I, incus; S, stapes; SC, semicircular canal; FO, foramen ovale; FR, foramen rotundum; ET, Eustachian tube; A, ampulla; V, vestibule and utricle; S, sacculus from which CR, the canal reuniens (cut across) connects with CC, the canal of the cochlea; SV, scala vestibuli; ST, scala tympani; 8 N, eighth nerve. In constructing the diagram the various structures have been shown in one plane, but actually the cochlea lies anterior to the semicircular canals. The lengthening of the basilar membrane towards the apex of the cochlea is shown in the left side only.

and the adjoining surface of the sphenoid, and from the sides of the canal in which the muscle lies; the tendon of the muscle bends at nearly a right angle over the end of the processus cochleariformis and is inserted into the inner part of the handle of the malleus. The *stapedius* is concealed within a canal in the bone in front of the aqueductus Fallopii. Its tendon is inserted into the neck of the stapes posteriorly.

The Internal Ear.—The proper organ of hearing is formed by the distribution of the auditory nerve, within the internal ear, or *laby-*

rinth, a set of cavities within the petrous portion of the temporal bone. The bone which forms the walls of these cavities is denser than that around it, and forms the *osseous labyrinth*; the membrane within the cavities forms the *membranous labyrinth*. The membranous labyrinth contains a fluid called *endolymph*; while outside it, between it and the osseous labyrinth, is a fluid called *perilymph*. This fluid is not pure lymph, as it contains mucin.

The **osseous labyrinth** consists of three principal parts, namely, the *vestibule*, the *cochlea*, and the *semicircular canals*.

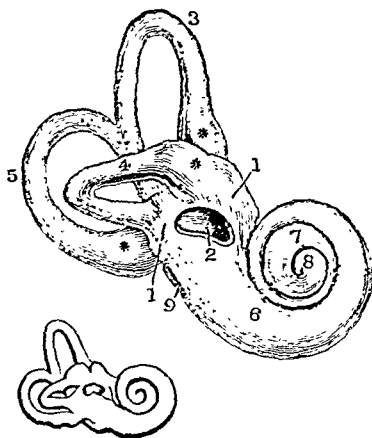


FIG. 245.—Right bony labyrinth, viewed from the outer side. The specimen here represented is prepared by separating piecemeal the looser substance of the petrous bone from the dense walls which immediately enclose the labyrinth. 1, The vestibule; 2, fenestra ovalis; 3, superior semicircular canal; 4, horizontal or external canal; 5, posterior canal; *, ampullæ of the semicircular canals; 6, first turn of the cochlea; 7, second turn; 8, apex; 9, fenestra rotunda. The smaller figure in outline below shows the natural size. $\frac{2\frac{1}{2}}{1}$. (Sömmering.)

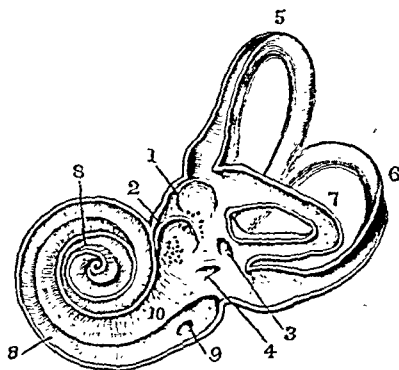


FIG. 246.—View of the interior of the left labyrinth. The bony wall of the labyrinth is removed superiorly and externally. 1, Recessus ellipticus; 2, Recessus sphericus; 3, common opening of the superior and posterior semicircular canals; 4, opening of the aqueduct of the vestibule; 5, the superior, 6, the posterior, and 7, the external semicircular canals; 8, spiral tube of the cochlea (scala tympani); 9, opening of the aqueduct of the cochlea; 10, placed on the lamina spiralis in the scala vestibuli. $\frac{2\frac{1}{2}}{1}$. (Sömmering.)

The *vestibule* is the middle cavity of the labyrinth, and the central chamber of the auditory apparatus. It presents, in its inner wall, several openings for the entrance of the divisions of the auditory nerve; in its outer wall, the *fenestra ovalis* (2, fig. 245), an opening filled by membrane, in which is inserted the base of the stapes; in its posterior and superior walls, five openings by which the *semicircular canals* communicate with it: in its anterior wall an opening leading into the *cochlea*. The *semicircular canals* have already been described in relation to Posture.

The **membranous labyrinth** corresponds in general form with the osseous labyrinth. The vestibule contains two membranous sacs, named the *utricle* and the *sacculæ* (fig. 247); the utricle

communicates with the three membranous semicircular canals; the saccule communicates with the utricle and with the *canal of the cochlea*. The vestibular division of the auditory nerve is distributed to the five spots shown in the diagram, namely, the maculæ of the utricle and saccule, and the cristæ of the semicircular canals. The cochlear division of the auditory nerve is distributed to the whole length of the canal of the cochlea.

The Cochlea.—This is shaped like a snail's shell. It is traversed by a central column or *modiolus*, around which a spiral canal winds with two and a half turns from base to apex. It is seen in vertical section that this canal is divided partly by bone (the *spiral lamina*), partly by membrane (the *basilar membrane*), into two spiral staircases or *scalæ*, the *scala tympani* and *scala vestibuli* (fig. 248). The *scala vestibuli* is separated from the tympanum by the membrane of the fenestra ovalis, and the *scala tympani* is similarly separated from the tympanum by the

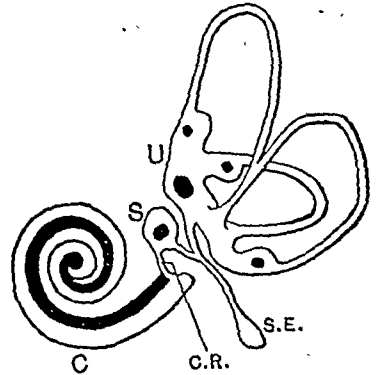


FIG. 247.—Diagram of the right membranous labyrinth. U, utricle, into which the three semicircular canals open; S, saccule, communicating with the cochlea (C) by C.R., the canalis reuniens, and with the utricle by a canal having on it an enlargement, the saccus endolymphaticus (S.E.) The black shading represents the places of termination of the auditory nerve, namely, in the maculæ of the utricle and saccule; the cristæ in the ampullary ends of the three semicircular canals; and in the whole length of the canal of the cochlea. (After Schafer.)

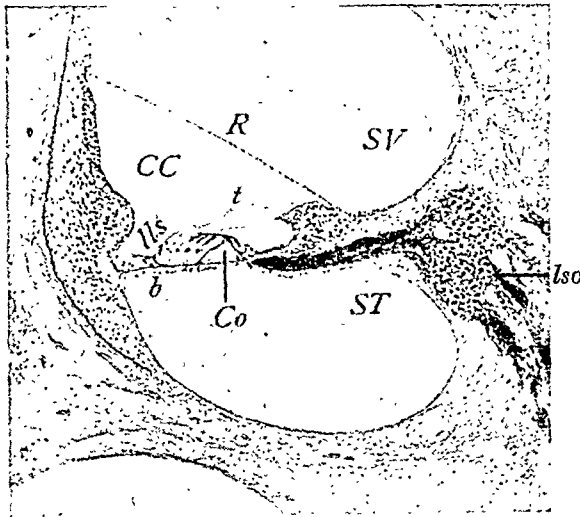


FIG. 248.—Section through one of the coils of the cochlea. ST, scala tympani; SV, scala vestibuli; CC, canalis cochleæ; R, membrane of Reissner; ls, lamina spiralis ossea; ls, limbus laminae spiralis; t, membrana tectoria (below the membrana tectoria is the lamina reticularis); b, membrana basilaris; Co, rods of Corti. (Hallpike.)

named the *helicotrema*, by which the two *scalæ*, separated in all the rest of their length, communicate.

membrane of the fenestra rotunda. Both *scalæ* are filled with perilymph. The basilar membrane increases in breadth from the base towards the apex of the cochlea. It contains fibres (about 24,000 in all) embedded in a homogeneous matrix and running radially, from the spiral lamina to the spiral ligament, where its other end is again attached to the bone. At the apex of the cochlea, the lamina ends in a small *hamulus*, the inner and concave part of which being detached from the summit of the modiolus, leaves a small aperture

Besides the scala vestibuli and scala tympani, there is a third space between them, called *scala media* or *canal of the cochlea* (CC fig. 248). In section it is triangular, its external wall being formed by the wall of the cochlea, its upper wall (separating it from the scala vestibuli) by the membrane of Reissner, and its lower wall (separating it from the scala tympani) by the basilar membrane; these two meet at the outer edge of the bony lamina spiralis.

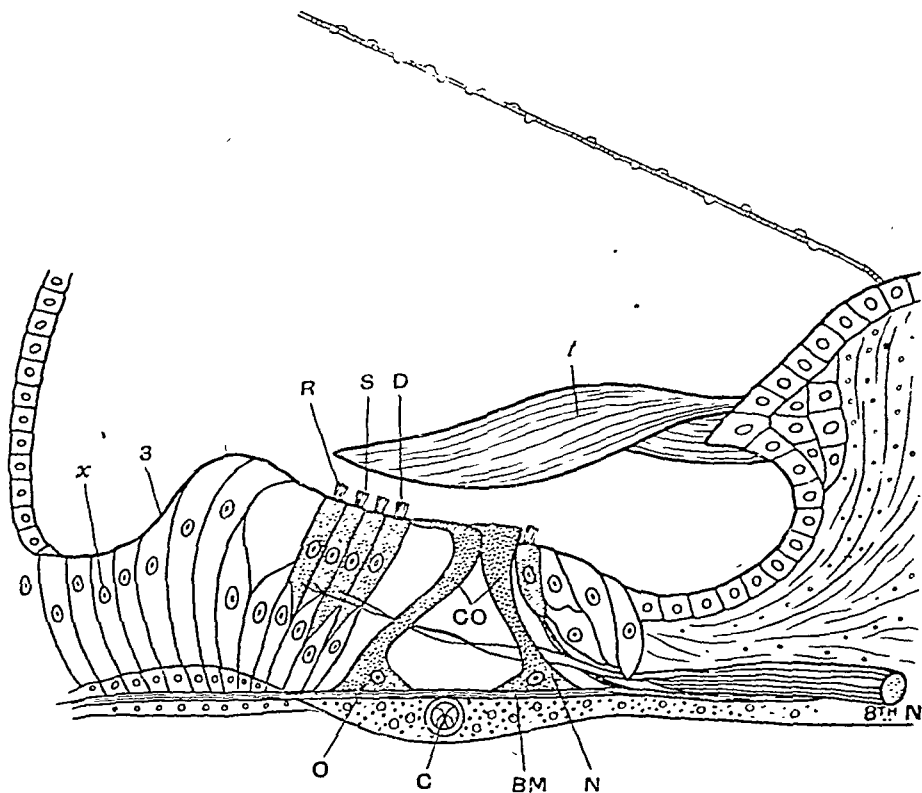


FIG. 249 — Diagram of a vertical section of the organ of Corti, BM, basal membrane which projects beyond the bony lamina spiralis; C, blood vessel; O, pillar of CO, the organ of Corti; RSD, hair cells; x, supporting cell of Deiters; 3, cell of lamina reticularis; t, membrana tectoria; 8th N, eighth nerve. (Drawn from photograph by J. A. Hewitt.)

Following the turns of the cochlea to its apex, the scala media there terminates blindly; at the base of the cochlea a narrow passage (canalis reuniens) unites it with the sacculle. The scala media (like the rest of the membranous labyrinth) contains *endolymph*.

Organ of Corti.—On the basilar membrane are arranged cells of various shapes. About midway between the outer edge of the lamina spiralis and the outer wall of the cochlea are situated the *rods of Corti*. Viewed sideways, they are seen to consist of an

external and internal pillar, each rising from an expanded foot or *base* attached to the basilar membrane (O, N, fig. 249). They slant inwards towards each other, and each ends in a swelling termed the *head*; the head of the inner pillar overlies that of the outer. Each pair of pillars forms a pointed roof arching over a space, and by a succession of them a tunnel is formed.

The pillars in proceeding from the base of the cochlea towards its apex progressively increase in length, and become more oblique; in other words, the tunnel becomes wider, but diminishes in height as we approach the apex of the cochlea. Leaning against the rods of

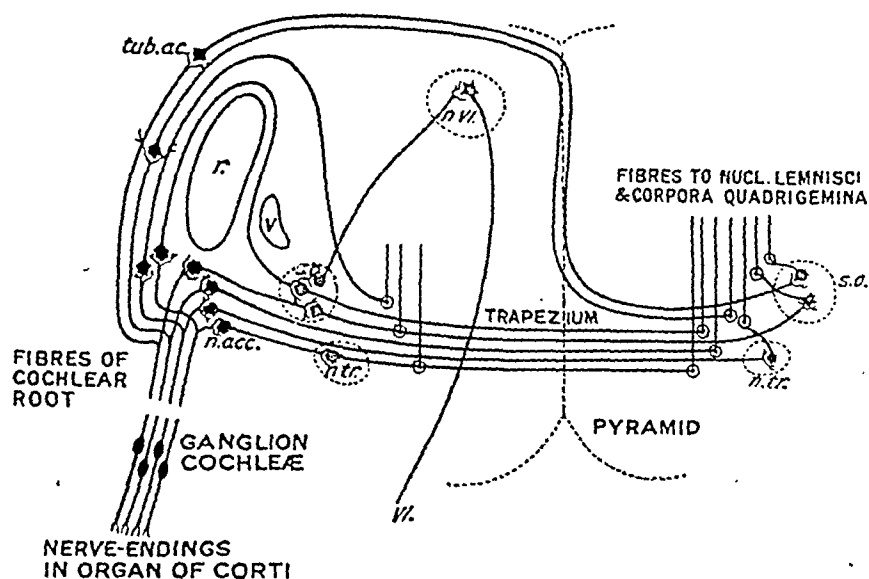


FIG. 250.—Cochlear division of the auditory nerve. *r.*, Restiform body; *V.*, descending root of the fifth nerve; *tub.ac.*, acoustic tubercle; *n.acc.*, accessory nucleus; *s.o.*, superior olive; *n.tr.*, trapezoid nucleus; *n.VI.*, nucleus of the sixth nerve; *VI.*, issuing fibre of sixth nerve. (Schafer.)

Corti are certain other cells called *hair-cells*, which terminate in small hair-like processes. There are several rows of these on the outer and one row on the inner side. Between them are certain supporting cells called *cells of Deiters* (fig. 249, *x*). The whole rests upon the basilar membrane; it is roofed in by a fenestrated membrane or lamina reticularis into the fenestræ of which the tops of the various rods and cells are received. When viewed from above, the organ of Corti shows a remarkable resemblance to the keyboard of a piano. Overhanging the organ is the *membrana tectoria* (fig. 249, *t*) which extends from the end of the limbus (*lls*, fig. 248), a connective-tissue structure on the spiral lamina. The *spiral ganglion* from which the cochlear nerve-fibres originate is situated in the spiral lamina.

Physiology of Hearing.

Sounds are caused by vibrations; when a piano-string is struck, it is thrown into a series of rapid regular vibrations; the more rapidly the vibrations occur the higher is the *pitch* of the musical note; the greater the amplitude of the vibration, the louder or more intense is the tone; if the vibrations are regular and simple (pendular), the tone is pure; if they are regular but compound, the tone is impure, and its quality or *timbre* is dependent on the rate and amplitude of the simple vibrations of which the compound vibrations are composed. The vibrations are transmitted as waves, and ultimately affect the hair-cells at the extremities of the auditory nerve in the cochlea. In the external ear the vibrations travel through air; in the middle ear through solid structures—membranes and bones; and in the internal ear through fluid.

This is the normal way in which the vibrations pass, but the endolymph may be affected in other ways, for instance through the other bones of the head; one can, for example, hear the ticking of one's watch when it is placed between the teeth, even when the ears are stopped. From this fact is derived a valuable practical method of distinguishing in a deaf person what part of the organ of hearing is at fault. The patient may not be able to hear a watch or a tuning-fork when it is held close to the ear; but if he can hear it when it is placed between his teeth, or on his forehead, the malady is localised in either the external or middle ear; if he can hear it in neither situation, it is a much more serious case, for then the internal ear or the nervous mechanism of hearing is at fault. In disease of the middle ear the hearing of low tones is especially affected; high tones appear to be transmissible by bone-conduction more readily than low.

In connection with the *external ear* there is not much more to be said; the pinna in many animals is large and acts as a kind of natural ear-trumpet to collect the vibrations of the air; in man this function is to a very great extent lost, and though there are muscles present to move it into appropriate postures, they are not under the control of the will in the majority of people, and are functionless, ancestral vestiges.

The Membrana Tympani.—This membrane, unlike that of ordinary drums, can take up and vibrate in response to an immense range of tones differing from each other by many octaves. This would clearly be impossible if it were an evenly stretched membrane. It is not evenly nor very tightly stretched, but owing to its attachment to the chain of ossicles it is slightly funnel-shaped: the ossicles also damp the continuance of the vibrations.

When the membrane gets too tightly stretched, by increase or decrease of the pressure of the air in the tympanum, then the sense of hearing is dulled. The pressure in the tympanic cavity is kept the same as that of the atmosphere by the *Eustachian tube*, which leads from the cavity to the pharynx, and so to the external air. The Eustachian tube is not, however, always open; it is opened by the action of the *tensor palati* during swallowing. When the tube is

closed—this often happens owing to swelling of the mucous membrane in inflammation of the throat—an interchange of gases takes place between the imprisoned air and the blood of the tympanic vessels. In time, as in the aërotonometer, equilibrium is established and the tension of the imprisoned gases becomes equal to that of the blood gases, not to that of the atmosphere. The membrane is therefore cupped inwards by the atmospheric pressure on its exterior; it is by this increased tightening of the membrane that deafness is produced. There is also an accumulation of mucus. When one makes a violent expiration, as in sneezing, some air is often forced through the Eustachian tube into the tympanum. The ears feel as though they were bulged out, as indeed the membrana tympani is, and there is again partial deafness, which sensations are at once relieved by swallowing, so as to open the Eustachian tube and thus re-establish equality of pressure.

The ossicles communicate the vibrations of the membrana tympani to the membrane which closes the fenestra ovalis (to which the foot of the stapes is attached). Thus the vibrations are communicated to the fluid of the internal ear, which is situated on the other side of the oval window.

The handle of the malleus vibrates with the membrana tympani; and the vibrations of the whole chain take place round the axis of rotation AB (fig. 251). Every time C comes forward D comes forward; but by drawing perpendiculars from C and D to the axis of rotation, it is found that D is about $\frac{2}{3}$ of the distance from the axis that C is. So in the transmission of the vibrations from membrane to membrane across the bony chain, the amplitude of the vibration is decreased by about $\frac{1}{3}$, and the force is correspondingly increased. This increase of power is augmented by the fact that the tympanic membrane concentrates its power upon an area (the membrane of the oval window) only one-twentieth of its size. The final movement of the stapes is, however, always very small; it varies from $\frac{1}{15}$ to less than $\frac{1}{10000}$ of a millimetre.

In one direction the ossicles move as if they were one. The advantage of their being several is that movements which move the membrane outwards do not move the incus. The increase of pressure on the inner side of the tympanic membrane caused by blowing the nose, therefore, is not communicated to the cochlea.

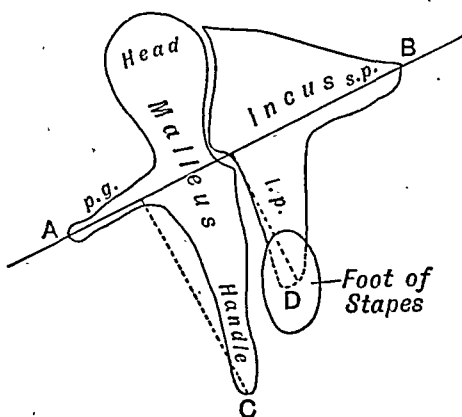


FIG. 251.—Diagrammatic view of ear ossicles.

The action of the *tensor tympani*, by pulling in the handle of the malleus, increases the tension of the *membrana tympani*. It is supplied by the fifth (trigeminal) nerve. It is opposed by the strong external ligament of the malleus. The *stapedius* attached to the neck of the stapes tilts it backwards and diminishes the intra-tympanic air-pressure. It is supplied by the seventh (facial) nerve.

The next very simple diagram (fig. 252) will explain the use of the *fenestra rotunda*.

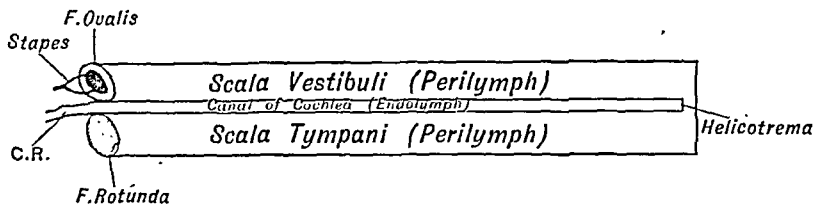


FIG. 252.—Diagram to illustrate the use of the fenestra rotunda. The intervention of the vestibular perilymph between the f. ovalis and the scala vestibuli is not shown.

The cochlea is supposed to be uncoiled; the scala vestibuli leads from the vestibule, in which is situated the fenestra ovalis, to the other side of which the stapes is attached; the scala tympani leads to the fenestra rotunda; the two scalæ communicate at the helicotrema, and are separated from the canal of the cochlea by the basilar membrane, and the membrane of Reissner. C. R. is the canalis reuniens leading to the sacculæ. The cochlea is filled with incompressible fluid in an inexpandible bony case, except where the windows are closed by membranes. Hence every time the membrane of the oval window is bulged in by the stirrup, the membrane of the round window is simultaneously bulged out to the same extent, and *vice versa*. These changes of pressure are transmitted from one scala to the other directly through the cochlear canal, which is set into vibration, and through the helicotrema.

The Analysis of Sound.

It is now generally agreed that the appreciation of sound depends on the basilar membrane. This membrane, as we have seen, separates the scala tympani from the canal of the cochlea and it is evident that it may be caused to vibrate by pressure waves set up in the perilymph of the scala tympani. The wave movements of the perilymph are made possible by the flexibility of the membrane closing the foramen rotundum. There have, however, been different opinions as to how and where the analysis of the sound takes place. It has been suggested (Rutherford and Wrightson) that the basilar membrane vibrates like a telephone receiver and impulses are set up which are conveyed to the brain as by telephone, the actual

analysis taking place in the brain. This appears unlikely, as, on one hand, we know of no cerebral mechanism by which such an analysis would take place and it has been calculated that the nerve could not carry the required number of impulses because of its refractory period. Moreover, it would not seem necessary to have such an elaborate structure as the cochlea for such a function. It has also been suggested (Waller-Ewald) that the basilar membrane itself might analyse such wave patterns according to the different parts thrown into motion. This avoids the difficulties suggested in relation to the Rutherford hypothesis, but like the latter cannot explain the loss of the power to recognise certain groups of notes when the membrane is injured in certain parts.

The view which is now most generally accepted is that originally put forward by Helmholtz that the different parts of the basilar membrane can vibrate in resonance with a particular wave to which they are, as it were, tuned, just as a wire of a piano can be made to sound if a note of suitable pitch is struck on another instrument. Helmholtz (1821-1894), trained originally in Medicine, became Professor of Physiology but later Professor of Physics in Berlin and one of the great physicists of his day.

Helmholtz's view is based on the fact that the fibres of the basilar membrane vary appreciably in length, its longest fibres at the apex of the cochlea being more than three times the length of those at the base, while the structures attached to the upper part of membrane have probably more than ten times the mass of those attached below. Between, the structures are intermediate. The long fibres vibrate to notes of 40 vibrations per second only, while the short fibres vibrate to those of 4000 per second. Support to this view is given by the result of damage to the cochlea. Animals in which conditioned reflexes have been established to low notes lose these reflexes if the apex is removed. Boilermakers who become deaf to high notes show degeneration of the base of the cochlea, and similarly it is claimed that prolonged subjection of an animal to a certain sound leads to a corresponding cochlear degeneration. It has further been found possible to make a model which will respond in a way similar to that suggested for the cochlea.

Hartridge has introduced a number of very interesting experiments which do much to support the Helmholtz theory. He has compared the changes in a telephone circuit with what occurs when a system of resonators is activated. In each case what is heard by the ear corresponds to what happens in a series of resonators. For example, the changing of the phase of a musical note by half a cycle does not alter the voltage in a telephone circuit; but to the ear there is a momentary interruption at the point of

change just as would occur if a tuned structure were caused to perform resonant vibrations. Also short interruptions of a musical sound which would be indiscernible to the ear or in the responses of series of resonators are quite evident in the current of a telephone circuit.

It may be considered that the vibration of the basilar membrane causes a movement of the hair cells which rest upon it. The actual stimulation probably takes place as a result of the contact of the hair cells with the tectorial membrane which rests upon them. In these cells are the endings of the auditory nerve which convey the impulses to the brain where their significance is appreciated. It is not, however, to be imagined that only one fibre of the basilar membrane vibrates at a time, rather we must presume that banks of fibres vibrate in harmony with the tones and overtones which stimulate the membrane.

What is virtually a complete proof of the Helmholtz theory has been obtained from a study of the action potentials set up in the auditory nerve and the finding of a spatial representation of the basal membrane on the surface of the cerebrum (see below). It has been shown (Adrian) that sounds of various pitches do *not* send impulses of any special frequencies, but that, as in the case of other afferent impulses, the frequencies set up depend on the intensity of the stimulus, *i.e.* the loudness of the sound.

The Auditory Pathways.

The fibres of the cochlear nerve take origin from the bipolar nerve-cells of the spiral ganglion of the cochlea; the peripheral axons ramify among the hair-cells of the organ of Corti, and the central axons pass towards the pons; as they enter they bifurcate, and some pass to and arborise round a collection of nerve-cells situated between the two roots and the restiform body, called the *accessory auditory nucleus*; the remaining fibres terminate similarly in a collection of cells in the grey matter overlying the restiform body, and extending into the ventricular floor in its widest part. This is called the ganglion of the root, and the mass of grey matter is termed the *acoustic tubercle*. The auditory path is continued by new axons that arise from these cells. Those from the accessory nucleus enter the trapezium, and pass in it partly to the superior olive and trapezoid nucleus of the same side, but mainly to the corresponding nuclei of the opposite side; some fibres end here, others traverse the nuclei, and merely give off collaterals to them; they then turn upwards in the lateral fillet, and so reach the inferior corpus quadrigeminum. The fibres which arise in the acoustic tubercle pass superficially over the floor of the ventricle, forming the *striae acusticae*; having crossed the raphé, they join the fibres from

the accessory nucleus in their course to the superior olive and fillet. Here again, however, a few fibres pass to the fillet of the same side. Fibres from the superior olive reach the nucleus of the sixth nerve and through the posterior longitudinal bundle the third and fourth nerve nuclei. Their presence partly explains movements of the eye in response to a sound. The lateral fillet communicates with the inferior corpus quadrigeminum and the medial geniculate body. From the latter the auditory radiation is distributed to the upper surface of the superior temporal gyrus concealed within the lateral fissure (Sylvius).

From quite a small area of this gyrus it has been found possible to record, in the monkey, the action potentials set up by various sounds, an area for low notes being at one end and another for high notes at the other.

Range of Hearing.

The range of hearing extends over 10 or 11 octaves; the lowest audible tone having about 20, the highest about 25,000, vibrations per second. The range varies in different people, and diminishes from childhood onwards. The upper limit of hearing may be tested by minute tuning-forks, metal rods, or by Galton's whistle. Many animals appear to be able to detect high tones which lie beyond the human limit. The lower limit may be determined by very large tuning-forks, or by employing very low difference-tones, but nowadays in all accurate work the audiometer is used (see below).

Difference-tones are produced when two tones of different pitch, m and n , are sounded together. A tone having the pitch m minus n is then heard in addition to the tones m and n : also a summation tone of pitch m plus n may be heard, but with greater difficulty. When m and n are nearly equal, a beating tone, instead of a difference-tone, results, having a pitch somewhere intermediate between m and n . If the difference between m and n is exceedingly small, this beating-tone alone is heard. The frequency of the beats corresponds to the difference in vibration-rates, m and n . Under certain conditions the difference and summation-tones (which are collectively called combination-tones) exist in the air; their presence is demonstrable by their reinforcement before appropriate resonators. More generally, however, they appear to be produced within the ear, *i.e.*, they have merely a subjective origin. The smallest perceptible difference in pitch between two successive tones is about 0.2 vibrations in the middle region of the piano for trained subjects. Practice effects extraordinary improvement, even among the most unmusical.

It should be noted that the ear is more sensitive to sounds of certain pitches than to others, as the eye is more sensitive to certain parts of the spectrum *e.g.*, sounds from 1000 to 2000 cycles,

i.e., just above average singing range low G 198 to high G 792. Loudness is, therefore, not strictly synonymous with sound intensity.

Sound location depends partly on the possession of two ears. The sound reaches the nearer ear first and thus difference in time is recognised.

Auditory Efficiency.

There is little doubt that auditory efficiency varies much more than is commonly recognised. This has become apparent by the introduction of more accurate means of measurement made possible by the use of the microphone and the audiometer (see below).

The **decibel** has been introduced as a convenient unit of loudness. It is a tenth of a *bel*, so-called after Graham Bell who

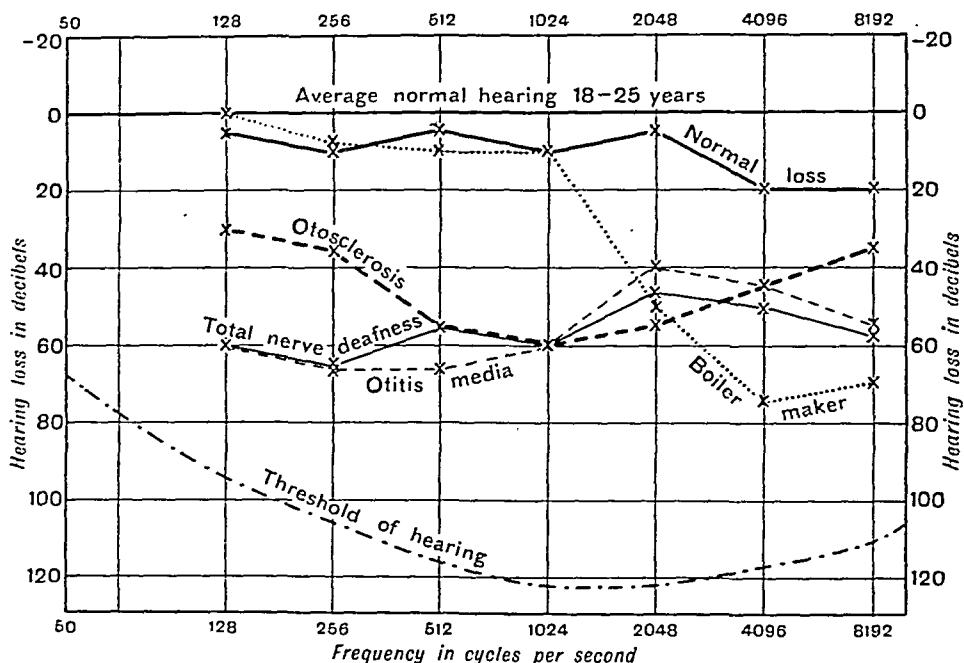


FIG. 253.—Audiometer records. Note specially the loss of the higher notes in boilermakers disease. (E. D. Dickson.)

invented the telephone. The decibel scale is a scale relative to the faintest audible sound thus:

Faintest audible	0	Thunder	70
Whisper at 4 feet	20	Loud motor horn at 23 feet .	100
Quiet street	30	Limit of endurance	130
Noisy street	60-80		

The actual scale is logarithmic; 1 bel is 10 times 0, 2 bels are 100 times 0. The scale really measures changes in the intensity of

a sound, and is used simply for convenience as the range of intensities is so great.

The audiometer is a thermionic valve apparatus from which pure tones of different pitch, but of the same intensity, can be delivered. It is possible to obtain audiometric curves from subjects which give an idea of the efficiency of the auditory apparatus at different pitches, which may be important in the selection of telephonists. By its use the differences produced by different lesions of the ear may be demonstrated, as seen in fig. 253. Since ordinary conversation takes place between 20 and 40 decibels, a person suffering from otosclerosis or damage to his nerve mechanism will complain of deafness but a boilermaker may not.

Obstruction in the external auditory meatus by plugging tends to cut out notes of high frequency which are most easily attenuated. For a similar reason we can hear the low notes of distant conversation or of the radio although we may not recognise what is said, (Fletcher, 1929; Beatty, 1932; Wever, 1933; Stevens, 1938.)

CHAPTER LVI

THE EYE AND VISION

THE eyeball, together with vessels and nerves, muscles to move it, and a quantity of adipose tissue, is contained in the orbit. In the front of the eyeball are the lids and lachrymal apparatus.

The *eyelids* consist of two movable folds of skin, each of which is kept in shape by a thin plate of fibrous tissue called the *tarsus*. Along their free edges are inserted a number of curved hairs (*eyelashes*), which, when the lids are half closed, serve to protect the eye from dust and other foreign bodies: the tactile sensibility of the lids is very delicate. Embedded in the tarsus are a number of long sebaceous glands (*Meibomian* or *tarsal*), the ducts of which open near the free edge of the lid. In the loose connective tissue in front of the tarsus, the bundles of the orbicularis muscle are situated.

The orbital surface of each lid is lined by a delicate, highly sensitive mucous membrane (*conjunctiva*), which is continuous with the skin at the free edge of each lid, and after lining the inner surface of the eyelid is reflected on to the eyeball, being somewhat loosely adherent to the sclerotic coat or sclera. Its epithelium, which is columnar, is continued over the cornea as its anterior epithelium, where it becomes stratified. At the inner edge of the eye the conjunctiva becomes continuous with the mucous lining of the lachrymal sac and duct, which again is continuous with the mucous membrane of the nose.

The eyelids are closed by the contraction of a sphincter muscle (*orbicularis*), supplied by the facial nerve; the upper lid is raised by the *levator palpebræ superioris*, supplied by the third nerve.

The *lachrymal gland*, composed of lobules made up of acini resembling the serous salivary glands, is lodged in the upper and outer angle of the orbit. Its secretion, which issues from several ducts on the inner surface of the upper lid, under ordinary conditions just suffices to keep the conjunctiva moist. It passes out through two small openings (*puncta lacrimalia*) near the inner angle of the eye, one in each lower lid, into the lachrymal sac, and thence along the nasal duct into the inferior meatus of the nose. The excessive secretion poured out under the influence of an irritating vapour or painful

emotion overflows the lower lid in the form of tears. The secretory nerves are contained in the lachrymal and temporo-malar branches of the fifth nerve, and in the cervical sympathetic.

The Eyeball.

The eyeball (fig. 254) consists of the following structures:—

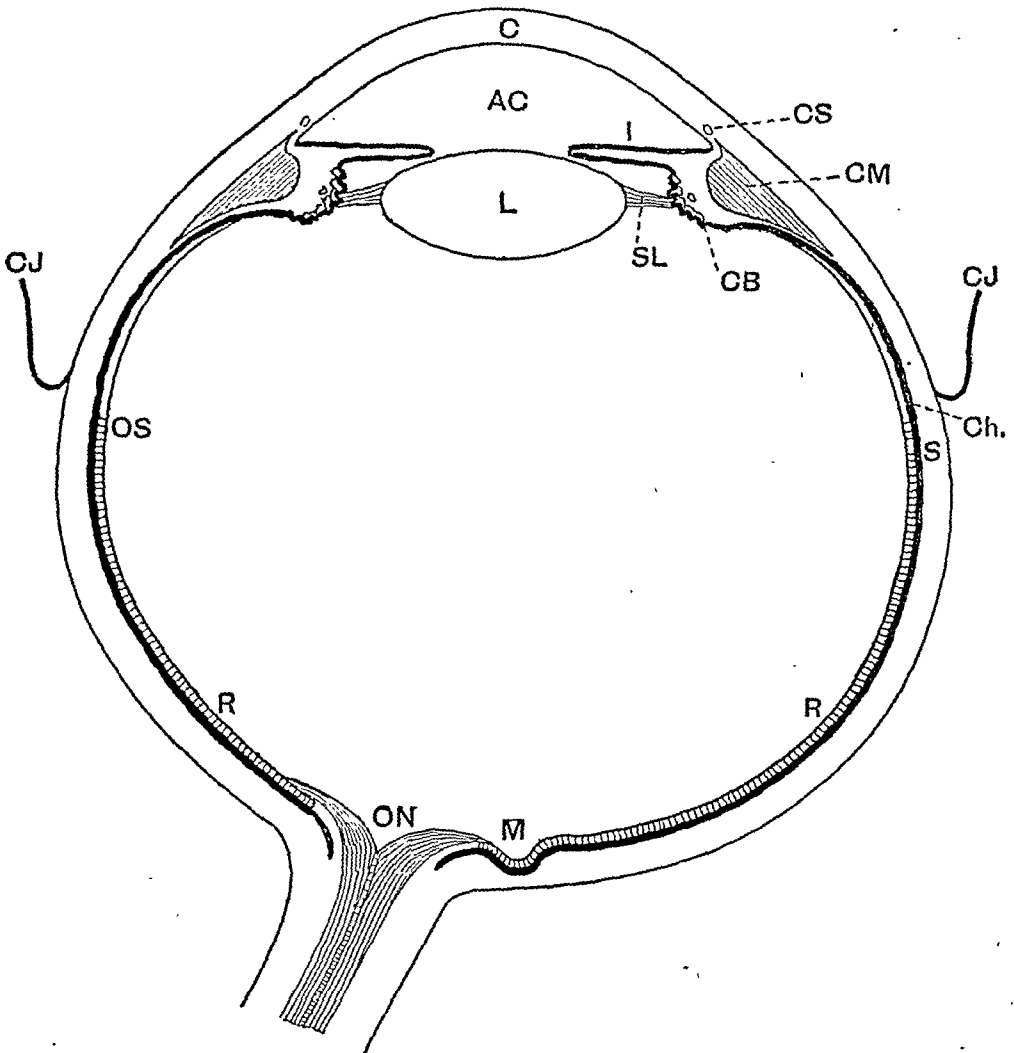


FIG. 254.—Diagram of eye. C, cornea; AC, anterior chamber; I, iris; L, lens; CS, canal of Schlemm; CM, ciliary muscle; SL, suspensory ligament; CB, ciliary body; CJ, conjunctiva; Ch., choroid; S, sclerotic; R, retina; M, macula or fovea centralis; ON, optic nerve; OS, ora serrata.

The *Sclera* or *Sclerotic*, the outermost coat, is made of white fibrous tissue and envelops about five-sixths of the eyeball: continuous with it, in front, and occupying the remaining sixth, is the transparent *cornea* (fig. 254). Immediately within the sclerotic is the *choroid* coat, and within the choroid is the *retina*. The interior of the eyeball

is filled by the *aqueous* and *vitreous humours* * and the *crystalline lens*; but, also, there is suspended in the interior a contractile and perforated curtain, the *iris*, which is continuous with the choroid; it regulates the admission of light; at the junction of the sclera and cornea is the ciliary muscle, the function of which is to adapt the eye for seeing objects at various distances.

The *Choroid Coat* is the vascular coat of the eyeball, and its connective tissue contains abundance of branched pigment cells.

The choroid coat ends in front in what is called the *ciliary body* (fig. 254) which is made up of blood-vessels, fibrous connective tissue, and pigment corpuscles. The ciliary processes terminate at the margin of the lens. The *ciliary muscle* takes origin at the corneo-scleral junction. It is a ring of muscle made up of fibres running in three directions: (a) Meridional fibres near the sclera and passing to the choroid; (b) radial fibres inserted into the choroid behind the ciliary processes; and (c) circular fibres (muscle of Müller), more internal; they constitute a sphincter.

The ciliary bodies also contain the ciliary processes which project slightly towards the interior of the eye. They are covered by a thin pigmented epithelium and are rich in capillaries.

From these structures is produced the aqueous humour or watery fluid of the anterior chamber of the eye.

The *Iris* is a continuation of the choroid inwards beyond the ciliary processes. It is a fibro-muscular membrane perforated by a central aperture, the pupil.

Posteriorly is a layer of pigment cells (*uvea*), which is a continuation forwards of the pigment layer of the choroid. The iris proper is made of connective tissue in front with corpuscles which may or may not be pigmented, and behind of similar tissue supporting blood-vessels. Surrounding the pupil is a layer of circular unstriped muscle, the *sphincter pupillæ*. There are also muscle-fibres which radiate from the sphincter in the substance of the iris forming the *dilator pupillæ*. The iris is covered anteriorly by a layer of epithelium continued upon it from the posterior surface of the cornea.

The *Lens* is situated behind the iris, being enclosed in a distinct capsule, the posterior layer of which is not so thick as the anterior. It is supported in place by the suspensory ligament, fused to the anterior surface of the capsule.

The lens is made up of a series of concentric laminae (fig. 255), which, when it has been hardened, can be peeled off like the coats of an onion. The laminae consist of long ribbon-shaped fibres, which in the course of development have originated from cells. The fibres are united by a scanty amount of cement substance. The central portion (*nucleus*) of the lens is the hardest.

* Sometimes called the vitreous body.

The epithelium of the lens consists of a layer of cubical cells anteriorly, which merge at the equator into the lens fibres. The development of the lens explains this transition.

Corneo-scleral Junction.—At this junction the relation of parts (fig. 254) is so important as to need a short description. In this neighbourhood, the iris and ciliary processes join with the cornea. The proper substance of the cornea and the posterior elastic lamina become continuous with the iris, at *the angle of the iris*, and the iris sends forwards processes towards the posterior elastic lamina, forming the *ligamentum pectinatum iridis*, and these join with fibres of the elastic lamina. The epithelial covering of the posterior surface of the cornea is, as we have seen, continuous over the front of the iris. At the iridic angle, the compact inner substance of the cornea is looser, and between the bundles are lymph spaces called the *spaces of Fontana*. They are but little developed in the human cornea.

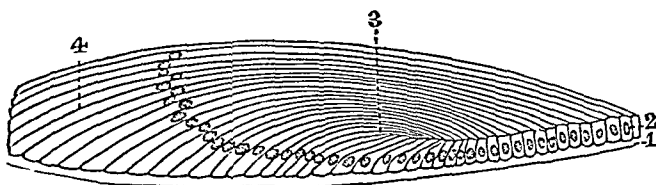


FIG. 255.—Meridional section through the part of the lens of a rabbit. 1, Lens capsule; 2, epithelium of lens; 3, transition of the epithelium into the fibres; 4, lens fibres. (Bubuchin.)

The spaces between the bundles of corneal tissue at the angle of the iris are continuous with the larger lymphatic space of the anterior chamber. Above the angle at the corneo-scleral junction is a canal, which is called the *canal of Schlemm*. It is a venous channel.

The Retina apparently ends in front, near the outer part of the ciliary processes, in a finely-notched edge—the *ora serrata*—but is really represented by the uvea to the very margin of the pupil. The nerve-cells in the retina remind us that the optic, like the olfactory nerve, is not a mere nerve, but an outgrowth of the brain.

In the centre of the retina is a round yellowish elevated spot, about 1 mm. in diameter, having a depression in the centre, called the *macula lutea* or *yellow spot*. The depression in its centre is called the *fovea centralis*. About 2.5 mm. to the inner side of the yellow spot is the point (*optic disc* or *white spot*) at which the optic nerve leaves the eyeball. The optic nerve-fibres are the axons of the nerve-cells of the retina; the dendrons of these cells ultimately communicate with the visual nerve-epithelium (rods and cones).

The optic nerve passes backwards to the ventral surface of the brain enclosed in prolongations of the membranes, which cover the brain. This external sheath at the exit of the nerve from the

eyeball becomes continuous with the sclera, which at this part is perforated by holes to allow of the passage of the optic nerve-fibres, the perforated part being the *lamina cribrosa*. The fibres of the nerve themselves are exceedingly fine, and are surrounded by the myelin sheath, but do not possess the ordinary external nerve sheath. In the centre of the nerve is a small artery, the *arteria centralis retinae*. The number of fibres in the optic nerve is said to be upwards of 500,000.

The retina consists of certain elements arranged in ten layers from within outwards (figs. 256, 257), and surprising as it may seem at first sight the light passes through most before reaching the sensitive nerve-endings.

1. *Membrana limitans interna*.—This so-called membrane in contact with the vitreous humour is formed by the junction laterally of the bases of the *sustentacular* or *supporting fibres* of *Müller*, which bear the same relation to the retina as the neuroglia does to the brain.

2. *Optic nerve-fibres*.—This layer is of very varying thickness in different parts of the retina; it consists of non-medullated fibres which interlace, and most of which are the axons of the large nerve-cells forming the next layer.

3. *Layer of ganglion cells*.—This consists of large multipolar nerve-cells with large and round nuclei, forming either a single layer, or in some parts of the retina, especially near the *macula lutea*, where this layer is very thick, it consists of several strata of nerve-cells. They are arranged with their single axis-cylinder processes inwards. These pass into and are continuous with the layer of optic nerve-fibres. Externally the cells send off several branched processes which pass into the next layer.

4. *Inner molecular layer*.—This presents a finely granulated appearance. It consists of neuroglia traversed by numerous fibrillar processes of the nerve-cells just described, and the minute branchings of the processes of the bipolar cells of the next layer.

5. *Inner nuclear layer*.—This consists chiefly of numerous small round cells, each with a very small quantity of protoplasm surrounding a large ovoid nucleus. The large oval nuclei (fig. 257) belonging to the Müllerian fibres occur also in this layer.

6. *Outer molecular layer*.—This layer closely resembles the inner molecular layer, but is much thinner. It contains the branchings of the rod and cone fibres on the one hand and of the bipolar cells on the other.

7. *External nuclear layer*.—This layer consists of small cells resembling at first sight those of the internal nuclear layer; they are classed as rod and cone granules, according as they are connected with the rods and cones respectively, and will be described with them.

8. *Membrana limitans externa*.—This is a well-defined membrane, marking the internal limit of the rod and cone layer, and made up of the junction of the sustentacular or Müllerian fibres externally.

9. *Layer of rods and cones*.—This layer is the nerve-epithelium of the retina. It consists of two kinds of cells, rods, and cones, which are arranged at right angles to the external limiting membrane, and supported by hair-like processes (*basket*) proceeding from the latter for a short distance (fig. 256).

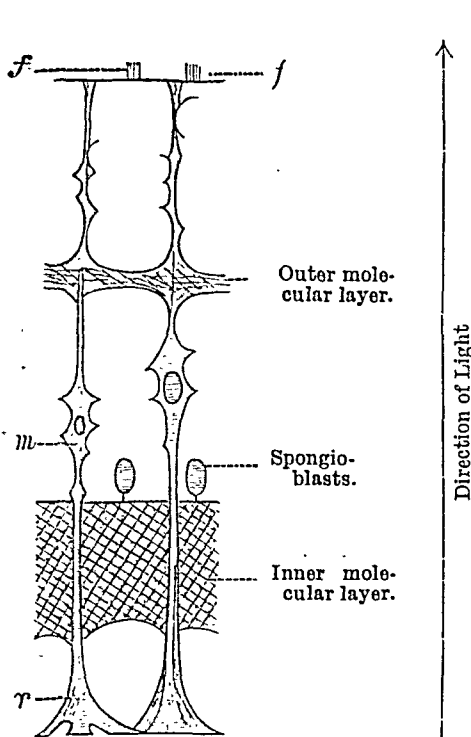


FIG. 256.—Diagram showing the sustentacular fibres of the retina; *f*, fibre-basket above the external limiting membrane; *m*, nucleus of the fibre; *r*, base of the fibre.

(From M'Kendrick, after Stöhr.)

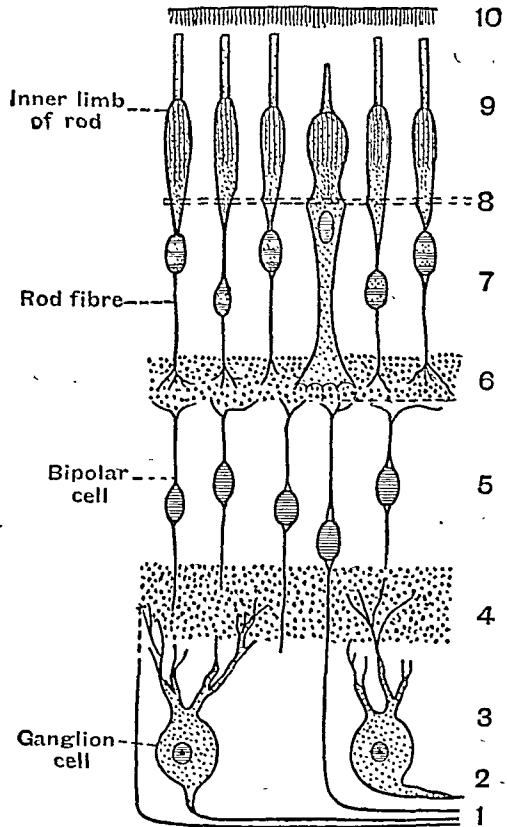


FIG. 257.—Diagram of retinal elements. In a section of the retina the pigment and molecular layers are most evident. (Modified from Schultze.) For explanation of numbers see text.

Each rod (fig. 257) is made up of two parts, very different in structure, called the outer and inner limbs. The outer limb of the rods is about 30μ long and 2μ broad, is transparent, and doubly refracting. It is said to be made up of fine superimposed discs. It stains brown with osmic acid but not with hæmatoxylin, and resembles in some ways the myelin sheath of a medullated nerve. It is the part of the rod in which the pigment called *visual purple* is found. In some animals a few rods have a greenish pigment instead.

The inner limb is about as long but slightly broader than the outer, is longitudinally striated at its outer, and granular at its inner part. It stains with hæmatoxylin, but not with osmic acid. Each rod is connected internally with a *rod fibre*, very fine, but here and there varicose; in the middle of the fibre is a *rod granule*, really the nucleus of the rod, striped broadly transversely, and situated about the middle of the external nuclear layer; the internal end of the rod fibre terminates in branchings in the outer molecular layer.

Each cone (fig. 257), like each rod, is made up of two limbs, outer and inner. The outer limb is tapering and not cylindrical like

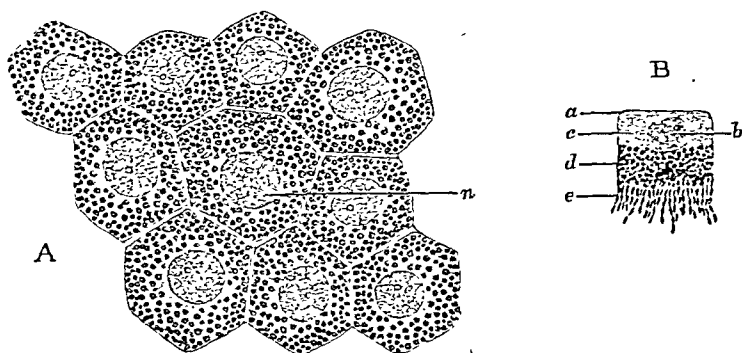


FIG. 25S.—Pigmented epithelium of retina (after Greeff). A, Surface view; *n*, nucleus. B, Single cell in profile view; *a*, free surface; *b*, nucleus; *c*, pigment-free cytoplasm; *d*, pigmented cytoplasm; *e*, pigmented processes.

the corresponding part of the rod, and about one-third only of its length. There is, moreover, no visual purple found in the cones. The inner limb of the cone is broader in the centre. It is protoplasmic, and under the influence of light has been seen to execute movements. In birds, reptiles, and amphibia, there is often a coloured oil globule present here. Each cone is in connection by its internal end with a *cone fibre*, which has much the same structure as the rod fibre, but is stouter and has its nucleus (*cone granule*) quite near to the external limiting membrane. Its inner end terminates by branchings in the external molecular layer.

In the rod and cone layer of birds, the cones usually predominate largely in number, whereas in man the rods are by far the more numerous, except in the fovea centralis, where cones only are present. The number of cones has been estimated at 3,000,000.

10. *Pigment-cell layer*.—This layer consists of a single layer of polygonal cells, which send down a beard-like fringe to surround the outer ends of the rods.

Note that this pigment layer which contains the visual purple

lies almost in contact with the pigment containing cells of the choroid coat of the eyeball which excludes the light. Between the two layers is the thin membrane of Bruch.

Differences in structure of different parts.—Towards the centre of the *macula lutea* all the layers of the retina become greatly thinned out and almost disappear, except the rod and cone layer, and at the *fovea centralis* the rods disappear, and the cones are long and narrow. At the margin of the fovea the layers increase in thickness, and in the rest of the *macula lutea* are thicker than elsewhere. The ganglionic layer is especially thickened, the cells being six to eight deep (2, fig. 259). Cone nuclei are obliquely disposed (fig. 259) on the course of the cone fibres, and are situated at some distance from the *membrana limitans externa*, which is cupped towards the fovea (fig. 259). The yellow tint of the macula is due to a diffuse colouring matter in the interstices of the four or five inner layers; it is absent at the centre of the fovea.

It is important to notice what is clearly brought out in fig. 257, that at the fovea each cone is connected to a separate chain of neurones, whereas in other regions the rods and cones are connected in groups to these chains; this explains the greater sensitiveness of foveal vision which has been confirmed by measurement of the excitability of the retina at different points.

At the *ora serrata* the layers are not perfect and disappear in this order: nerve-fibres and ganglion cells, then the rods, leaving only the inner limbs of the cones, next these cease, then the outer molecular layer, the inner and outer nuclear layers coalescing, and finally the inner molecular layer also is unrepresented.

At the *pars ciliaris retinae*, the retina consists of a layer of columnar cells, which probably represent the Müllerian fibres. These cells externally are in contact with the pigment layer of the retina, which is continued over the ciliary processes and back of the iris. Nervous structures are absent.

At the exit of the optic nerve the only structures present are nerve-fibres.

The **anterior chamber** is the space behind the cornea and in front of the iris. Between the iris and the lens is the **posterior chamber**.

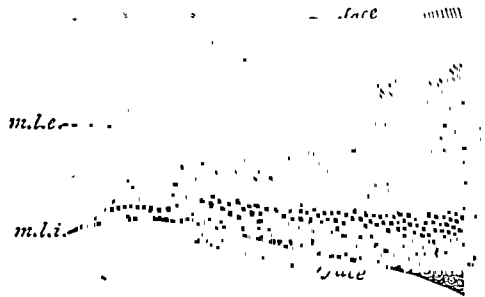


Fig. 259.—Diagram of a section through half the fovea centralis. 2, Ganglionic layer; 4, inner nuclear; 6, outer nuclear layer, the cone fibres forming the so-called *external fibrous layer*; 7, cones; *m.l.e.*, *membrana limitans externa*; *m.l.i.*, *membrana limitans interna*. (Schafer and Golding Bird.)

The Fluids of the Eye and Intraocular Pressure.

The chambers of the eye are filled with the aqueous humour. This fluid has the composition of dilute lymph, that is, it contains in solution the salts of the blood plasma but less protein. It is elaborated by the ciliary glands of the ciliary processes, and plays an important part in maintaining the intraocular pressure. (See Duke-Elder.)

The fluids in the eye are under a pressure of 20 to 30 mm. Hg, and may be measured accurately by plunging through the sclera a hollow needle attached to a manometer. The general tension of the eyeball can be appreciated also on oneself by palpation with two fingers. Clinically the pressure is measured by a tonometer in which a piston works against a standardised spring. In the condition of glaucoma the pressure may so increase that it interferes with the blood supply of the retina, and may cause blindness. The mode of formation and drainage of the fluid of the eye is therefore of much practical importance. The aqueous humour appears to be produced like lymph, its pressure depending on capillary pressure and the osmotic pressure of the blood rather than arterial pressure. As pointed out by Duke-Elder, since the pressure in the exit veins is greater than the intra-ocular pressure there is an equilibrium. Normally the fluids drain away, as indicated by the injection of dyes, in three ways.

1. By the the canal of Schlemm, into which open the spaces of Fontana at the outer edge of the iris (the filtration angle), and which is of great importance as a drainage area.

2. By the crypts on the anterior surface of the iris.

3. By passing backwards to the vitreous humour from which it reaches the retinal veins and lymphatics.

This drainage of the eye is of the greatest importance in glaucoma, a condition associated with increased intraocular pressure which leads to degeneration of the retina and to blindness.

The **vitreous humour**, which is a jelly-like connective tissue, is situated behind the *crystalline lens*. It is enclosed in the hyaloid membrane which in front is continuous with the capsule of the lens; round the edge of the lens the canal left is called the **Canal of Petit**, the membrane itself being the *Zonule of Zinn*. The hyaloid membrane separates the vitreous humour from the retina.

Blood-vessels of the Eyeball.—The eye is very richly supplied with blood-vessels. In addition to the conjunctival vessels which are derived from the palpebral and lachrymal arteries, there are at least two other distinct sets of vessels supplying the tunics of the eyeball.

- (1) These are the short and long *posterior* ciliary arteries which pierce the sclera in the posterior half of the eyeball, and the *anterior* ciliary which enter

near the insertions of the recti. These vessels anastomose and form a rich choroidal plexus; they also supply the iris and ciliary processes, forming a highly vascular circle round the outer margin of the iris and adjoining portion of the sclera. The distinctness of these vessels from those of the conjunctiva is well seen in the difference between the bright red of blood-shot eyes (conjunctival congestion), and the pink zone surrounding the cornea which indicates deep-seated ciliary congestion.

(2) The *retinal vessels* are derived from the *arteria centralis retinae*, which enters the eyeball along the centre of the optic nerve. They ramify all over the retina, in its inner layers. They can be seen by ophthalmoscopic examination.

The Eye as an Optical Instrument.

In a photographic camera images of external objects are thrown on a screen at the back of a box, the interior of which is painted black. In the eye, the camera is represented by the eyeball with its black pigment, the screen by the layer of rods and cones of the retina, and the lens by the refracting media. In the camera, the screen is enabled to receive clear images of objects at different distances, by an apparatus for focussing. The corresponding contrivance in the eye is called *accommodation*.

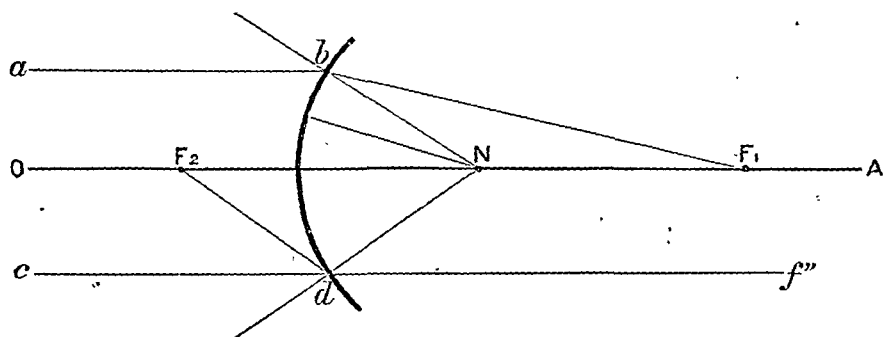


FIG. 260.—Diagram of a simple optical system (after M. Foster). The curved surface, *b d*, is supposed to separate a less refractive medium towards the left from a more refractive medium towards the right.

The iris, which allows more or less light to pass into the eye, corresponds with the diaphragms used in the photographic apparatus.

The refractive media are the cornea, aqueous humour, crystalline lens, and vitreous humour. The most refraction or bending of the rays of light occurs where they pass from the air into the cornea; they are again bent slightly in passing through the lens. Alterations in the anterior curvature of the lens lead to accommodation.

We may first consider the refraction through a transparent spherical surface, separating two media of different density.

The rays of light which fall on the surface exactly perpendicularly do not suffer refraction, but pass through, cutting the optic axis (O A, fig. 260), a line which passes exactly through the centre of the surface, at a certain point, the *nodal point* (fig. 260, N), or centre of curvature. Any rays which do not so strike the curved

surface are refracted towards the optic axis. Rays which impinge upon the spherical surface parallel to the optic axis meet on the optic axis at a point which is behind the nodal point and is called the *chief posterior focus* (fig. 260, F_1); and again there is a point on the optic axis in front of the surface, rays of light from which so strike the surface that they are refracted in a line $d f''$ parallel with the axis; this point (fig. 260, F_2) is called the *chief anterior focus*. The optic axis cuts the surface at the *principal point*.

It is quite obvious that the eye is a much more complicated optical apparatus than the one described in the figure. It is, however, possible to reduce the refractive surfaces and media to a simpler form when the refractive indices of the different media and the curvature of each surface are known. These data are as follows:—

Index of refraction of cornea	= 1.37
" " aqueous and vitreous	= 1.34 to 1.36
" " lens	= { 1.4 in outer to 1.45 in inner part.
Radius of curvature of cornea	= 7.8 mm.
" " anterior surface of lens	= 10 "
" " posterior	= 6 "
Distance from anterior surface of cornea to anterior surface of lens	= 3.6 "
Distance from posterior surface of cornea to posterior surface of lens	= 7.2 "
Distance from posterior surface of lens to retina	= 15.0 "

It is important to note that the cornea plays the greatest part in refraction in man although it is less important in fishes. With the aid of glasses a human being can still see quite well after the lens has been removed for cataract.

With these data it has been found comparatively easy to reduce, by calculation, the different surfaces of different curvature into one mean curved surface of known curvature, and the differently refracting media into one mean medium the refractive power of which is known.

The simplest so-called schematic eye formed on this principle, suggested by Listing as the *reduced schematic eye*, has the following more important dimensions:—

Retina lies behind cornea	= 22.8237 mm.
The nodal point lies in front of posterior surface of lens	= 0.4764 "
From the nodal point to retina, i.e. focal length	= 15.4700 "
Radius of ideal surface	= 5.1218 "

The term *index of refraction* means the ratio of the sine of the angle of incidence to that of the angle of refraction; this is explained in the small text beneath fig. 261.

In this reduced or simplified eye, the principal posterior focus, about **23 mm.** behind the spherical surface, would correspond to the position of the retina behind the anterior surface of the cornea. The refracting surface would be situated about midway between the

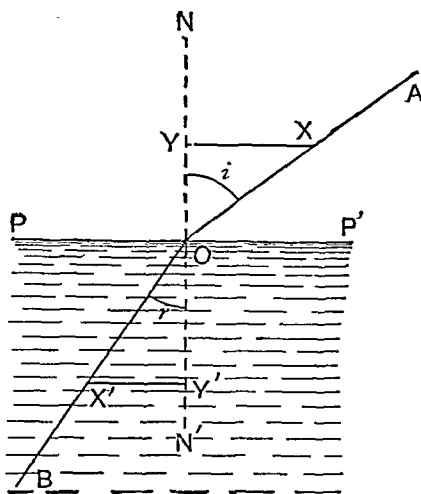


FIG. 261.—If $P P'$ is a line which separates two media, the lower one being the denser, and $A O$ is a ray of light falling on it, it is bent at O towards the normal or perpendicular line $N N'$. $A O$ is called the incident ray, and $O B$ the refracted ray; $A O N$ is called the angle of incidence (i), $N' O B$ the angle of refraction (r). If any distance $O X$ is measured off along $O A$, and an equal distance $O X'$ along $O B$, and perpendiculars drawn to $N N'$; then $\frac{X Y}{X' Y'} = \text{index of refraction}$.

posterior surface of the cornea and the anterior surface of the lens.

The *optical axis* of the eye is a line drawn through the centres of

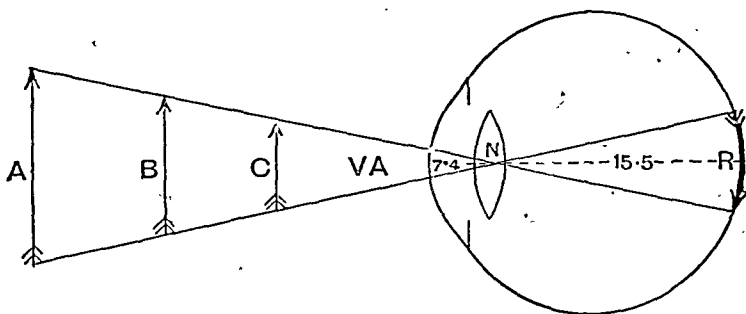


FIG. 262.—Diagram to show the formation of an image in the retina. VA , visual angle; N , nodal point; R , retina.

curvature of the cornea and lens, prolonged backwards to touch the retina between the optic disc and fovea centralis, and this differs from the *visual axis* which passes through the nodal point of the reduced eye to the fovea centralis; this forms an angle of 5° with the optical axis. But for practical purposes the optical axis and the visual axis may be considered to be identical.

The *visual* or *optical angle* (fig. 262) is included between the lines drawn from the borders of any object to the nodal point; if the lines are prolonged backwards they include an equal angle. It has been shown by Helmholtz that the smallest angular distance between two points which can be appreciated as two distinct points is 50 seconds, the size of the retinal image being 3.65μ ; this is a little more than the diameter of a cone at the fovea centralis which is 3μ , the distance between the centres of two adjacent cones being 4μ . If the two points are so close together that they subtend a visual angle less than 50 seconds, usually taken as 1 minute, both images will fall upon one cone, and the two points will therefore appear as one.

The Formation of a Retinal Image.—Any object, for example the arrow A B (fig. 262), may be considered as a *series of points*

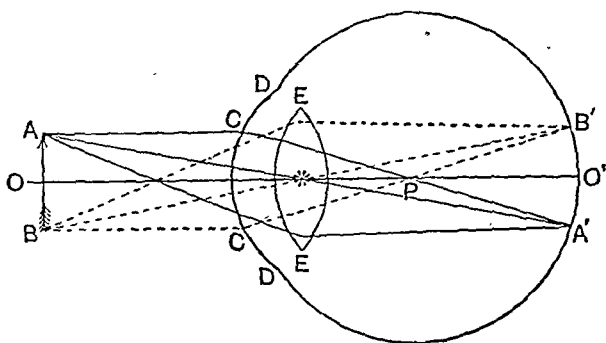


FIG. 263.—Diagram of the course of the rays of light, to show how an image is formed upon the retina in an *accommodating* eye. The surface C C should be supposed to represent the ideal curvature. In actual fact the rays are refracted not only at the cornea, but also at the surfaces of the lens and at the vitreous humours. In the unaccommodated eye the point P is on the retina. A and B are to be considered points from which rays of light radiate.

from each of which rays of light diverge towards the eye. Take, for instance, the rays diverging from the tip of the arrow A; C C represents the curvature of the schematic or reduced eye; the ray which passes through the centre of the lens system, *i.e.* the nodal point, is not refracted (the asterisk in fig. 263), it is near the posterior surface of the crystalline lens; the ray A C, which is parallel to the optic axis O O', is refracted through the principal posterior focus P, and cuts the first ray at the point A' on the retina. The other rays from A meet at the same point to form an image. Similarly, the other end of the arrow B is focussed at B' and rays from all other points have corresponding foci.

It will thus be seen that an inverted image of external objects is formed on the retina. The retina is a curved screen, but the images fall only on a small area of the retina under normal conditions; hence, for practical purposes, this small area may be regarded as flat.

The question then arises, Why is it that objects do not appear to

us to be upside down? This cannot be satisfactorily answered without entering into matters which require a previous psychological training. Suffice it to say here that the localisation of objects in space depends not only on the retina, but also on tactile and general experience; that the mind localises objects with reference to its own body, and that from the first it knows nothing of the inversion of the retinal image, as its powers of localisation only appear with developing general experience.

The **size of a retinal image** may readily be calculated as indicated by fig. 262, from a knowledge of the size of the object and its distance from the eye (nodal point), the distance of the nodal point from the image on the retina being taken as 15.5 mm. Thus an object 1 metre long and 5 metres from the eye produces an image x times the size of the object, which is $\frac{15.5}{7.4} \times$ the distance of the object from the cornea,

i.e. $1000 \times \frac{15.5}{5007.4} = 3$ mm. (approx.). In a similar way, by mapping out the blind spot on a blackboard a given distance away we may measure the size of the optic disc.

Accommodation.

The power of accommodation is primarily due to an ability to vary the shape of the lens; its front surface becomes more or less convex, according as the distance of the object looked at is near or far. The nearer the object, the more convex, up to a certain limit, the front surface of the lens becomes, and *vice versa*; the back surface takes no share in the production of the effect required. The posterior surface, which during rest is more convex than the anterior, is thus relatively the less convex of the two during accommodation. The following simple experiment illustrates this point: If a lighted candle is held a little to one side of a person's eye an observer looking at the eye from the other side sees three images of the flame (fig. 264). The first and brightest is (1) a small erect image formed by the anterior convex surface of the cornea; the second (2) is also erect, but larger and less distinct than the preceding, and is formed at the anterior convex surface of the lens; the third (3) is smaller, inverted, and indistinct; it is formed at the posterior surface of the lens, which is concave forwards, and therefore, like all concave mirrors, gives an inverted

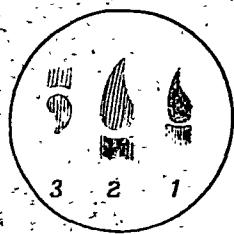


FIG. 264.—Diagram showing three reflections of a candle. 1, From the anterior surface of cornea; 2, from the anterior surface of lens; 3, from the posterior surface of lens.

image. If now the eye under observation is made to look at a near object, the second image becomes smaller, clearer, and approaches the first. If the eye is now adjusted for a far-point, the second image enlarges again, becomes less distinct, and recedes from the first. In both cases the first and third images remain unaltered in size, distinctness, and position. This proves that during accommodation for near objects the curvatures of the cornea, and of the *posterior surface* of the lens, remain unaltered, while the *anterior surface* of the lens becomes more convex and approaches the cornea.

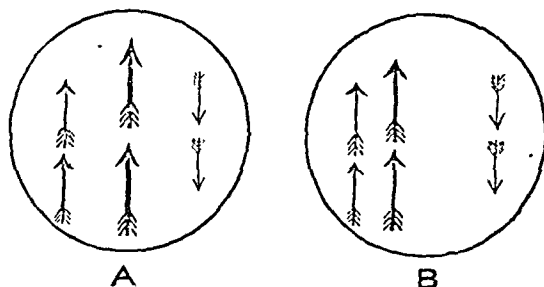


FIG. 265.—Diagram of Sanzon's images. A, when the eyes are not, and B, when they are focussed for near objects. The arrow to the right in A and B is the inverted image from the posterior surface of the lens.

The experiment is more striking when two bright images (represented by arrows in fig. 265) are used; the two images from the front surface of the lens during accommodation not only approach those from the cornea, but also approach one another, and become somewhat smaller. (*Sanzon's Images*.) Helmholtz's phakoscope (fig. 266) is a box with arrangements for demonstrating this experiment.

Mechanism of Accommodation.—The lens having no inherent power of contraction, its changes of outline must be produced by some power from without; this power is supplied by the ciliary muscle. Its action is to draw forwards the choroid, and by so doing to slacken the tension of the suspensory ligament of the lens which arises from it. The anterior surface of the lens is kept flattened by the action of this ligament. The ciliary muscle during accommodation, by diminishing the tension of this ligament, diminishes to a proportional degree the flattening of which it is the cause. On diminution or cessation of the action of the ciliary muscle, the lens returns to its former shape (fig. 267). From this it will appear that the eye is usually focussed for distant objects. In viewing near objects the ciliary muscle contracts; the ciliary muscle relaxes on withdrawal of the attention from near to distant objects.

During accommodation two other changes take place in the eyes:

- (1) *The eyes converge* owing to the action of the internal rectus muscle of each eyeball. (2) *The pupils contract.*

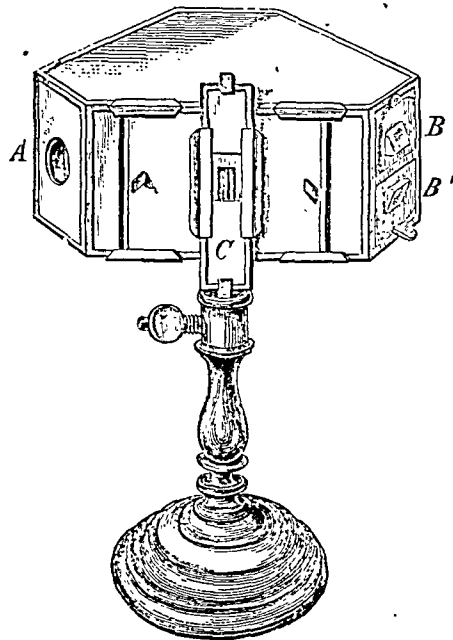


FIG. 265.—Phakoscope of Helmholtz. At *B B'* are two prisms, by which the light of a candle is concentrated on the eye of the person experimented with, which is looking through a hole in the third angle of the box opposite to the window *C*. *A* is the aperture for the eye of the observer. The observer notices three double images, represented by arrows, in fig. 265, reflected from the eye under examination when the eye is fixed upon a distant object; the position of the images having been noticed, the eye is made to focus a near object, such as a reed pushed up at *C*; the images from the anterior surface of the lens will then be observed to move as described in the text.

The contraction of all of the muscles which have to do with accommodation, viz., of the ciliary muscle, of the internal recti muscles, and of the sphincter pupillæ, is under the control of the

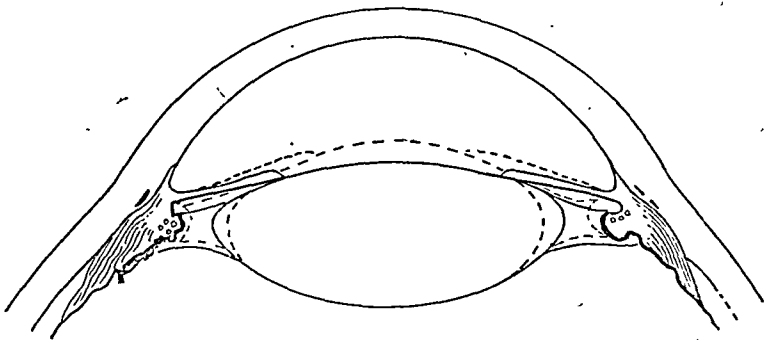


FIG. 267.—Diagram representing, by dotted lines, the alteration in the shape of the lens on accommodation for near objects. (E. Landolt.)

third nerve. It should further be noted that although the act is a voluntary one, the fibres of the ciliary muscle and of the sphincter pupillæ are of the plain variety.

The account of accommodation as given in the preceding pages is true for man and other mammals, some birds, and certain reptiles.

Beer has, however, shown that in many animals lower in the scale the mechanism of accommodation varies a good deal, and is often very different from that just described, consisting, in fact, in a power of altering the distance between the lens and the retina.

In bony fishes, the eye at rest is accommodated for near objects; in focussing for distant objects the lens is drawn nearer to the retina by a special muscle called the *retractor lentis*. In some molluscs the *retractor lentis* is absent and the approach of the lens to the retina is brought about by an alteration of intra-ocular tension. In amphibia and most snakes, the eye at rest is focussed for distant objects; in accommodating for near objects the lens, by alteration of intra-ocular tension, is brought forward, that is, the distance between it and the retina is increased. There appear to be not a few animals in all classes which do not possess the power of accommodation at all. Indeed Barrett states this is so for most mammals.

Range of Distinct Vision. Near-point.—In every eye there is a limit to the power of accommodation. If a book is brought nearer

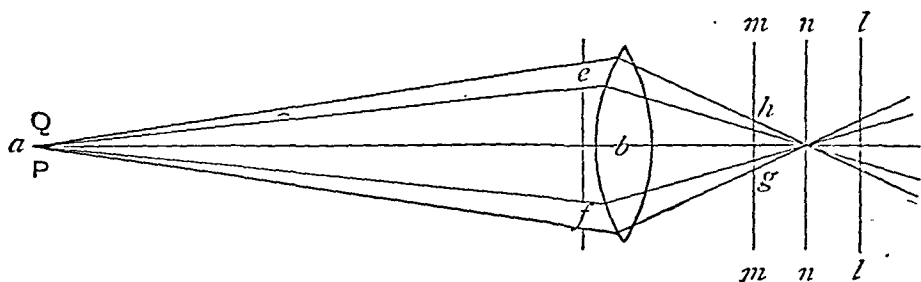


FIG. 268.—Diagram of experiment to ascertain the minimum distance of distinct vision.

and nearer to the eye, the type at last becomes indistinct, and cannot be brought into focus by any effort of accommodation, however strong. This, which is termed the **near-point**, can be determined by *Scheiner's* experiment. Two small holes are pricked in a card with a pin not more than a-twelfth of an inch (2 mm.) apart; at any rate their distance from each other must not exceed the diameter of the pupil. The card is held close in front of the eye and a small needle viewed through the pin-holes. At a moderate distance it can be clearly focussed, but when brought nearer, beyond a certain point, the image appears double. This point where the needle ceases to appear single is the near-point. Its distance from the eye can be readily measured. It is usually about 5 or 6 inches (13 cm.). In the accompanying figure (fig. 268) the lens *b* represents the refractive apparatus of the eye; *e* and *f* the two pin-holes in the card, *nn* the retina; *a* represents the position of the needle. When the needle is at a moderate distance, the two pencils of light coming through *e* and *f* are focussed at a single point on the retina *nn*. If the needle is brought nearer than the near-point, the strongest effort of accommodation is not sufficient to focus

the two pencils, they meet at a point behind the retina. The effect is the same as if the retina were shifted forward to *mm*. Two images *h*, *g* are formed, one from each hole. It is interesting to note that when two images are produced, the lower one *g* really appears in the position *q*, while the upper one appears in the position *p*. This may be readily verified by covering the holes in succession.

Visual Acuity.

In relation to the visual angle we have seen that unless two points are sufficiently apart they appear as one point on the retina. Use is made of this in testing visual acuity. This is done by means of test types (Snellen). Each letter is printed within a square which subtends an angle of 5 minutes at the distance of 6 metres (20 feet) at which the normal eye should distinguish the letter—and 25 smaller squares into which the square may be divided, each subtends an angle of 1 minute. The types are of different sizes like the arrows in fig. 265, the largest being that which can be distinguished at 60 metres and then follow rows of letters which should be read at closer distances.

The acuteness of vision is expressed by a fraction of which the numerator is 6 (*i.e.* the distance from the chart) and the denominator, the distance at which the smallest letters should be read by the normal eye. Thus normal vision *V* ought to be $V = \frac{6}{6}$. A subject with poorer vision might be expressed

as having $V = \frac{6}{18}$, that is, at 6 metres, the smallest type he can read is 18 or that which ought to be read at 18 metres' distance. By putting appropriate test lenses in spectacle-frames in front of the eye, the lenses necessary to bring the vision to normal may be found.

With a person such as a child a method independent of his answers is desirable and the method of retinoscopy is used. This is dealt with fully on p. 751.

Although in detailed work many tests have been elaborated, visual acuity is readily studied.

A most satisfactory test is the power to read print, but in patchy disease of the retina (scotoma) it is often quite remarkable what a degree of retinal damage may be present before there is any complaint of failure of vision because the subject learns to use unconsciously the healthy part only.

The near point gives information regarding the power of accommodation and indirectly of the power of the individual to discern small objects.

Normal persons should be able to read the following easily:—

Line 1 at 20 inches, line 2 at 30, and line 3 at 40; but there is little doubt that detailed work demands even higher degrees of visual efficiency. Some anthropologists hold that the development of visual efficiency together with stereoscopic vision has been chiefly responsible for the pre-eminence of the primates (Elliot-Smith).

D.=0.50

No. 1.	FELT	LEFT	FEEL	TELL
	COOL	LODE	CODE	DOLE
	DEFT	FLOE	LEET	FEET
	CLOD	COLT	DOLL	COOT

D.=0.75

No. 2.	LEE	ELL	ELF	FOE
	COD	TOD	COT	TOO
	FEE	LET	EEL	ELL
	ODD	COD	LOO	DOE

D.=1.00

No. 3.	FELL	TOLL	DELL
	DOLE	FOOL	TOLD
	FLED	LOLL	CELT
	COLD	FOOD	DOFF

Defects in the Optical Apparatus.

Under this head we may consider the defects known as (1) Myopia, (2) Hypermetropia, (3) Astigmatism, (4) Spherical Aberration, (5) Chromatic Aberration, and (6) Presbyopia.

The normal (*emmetropic*) eye is so adjusted that at rest parallel rays are brought exactly to a focus on the retina. Hence all objects except near ones (practically all objects more than twenty feet off) are seen without any effort of accommodation; in other words, the far-point of the normal eye is at an infinite distance. In viewing near objects we are conscious of the effort (the contraction of the ciliary muscle) by which the anterior surface of the lens is rendered more convex, and rays which would otherwise be focussed *behind* the retina are converged upon the retina.

1. **Myopia** (short-sight).—This defect is due to an abnormal elongation of the eyeball. The retina is too far from the lens, and consequently parallel rays are focussed *in front of* the retina, and, crossing, form little circles on the retina; thus the images of distant objects are blurred and indistinct. The eye is, as it were, permanently adjusted for a near-point. Rays from a point near the eye are exactly focussed on the retina. But those which issue from

any object beyond a certain distance (*far-point*) cannot be distinctly focussed. This defect is corrected by *concave* glasses which cause the rays entering the eye to diverge: hence they do not come to a focus so soon. Such glasses, of course, are only needed to give a clear vision of distant objects. For near objects, except in extreme cases, they are not required.

2. **Hypermetropia.**—This is the reverse defect. The eyeball is too short. Parallel rays are focussed *behind* the retina: an effort of accommodation is required to focus even parallel rays on the retina; and when they are divergent, as in viewing a near object, the accommodation is insufficient to focus them. Thus, in well-marked cases, distant objects require an effort of accommodation, and near ones a very powerful effort, and the ciliary muscle is, therefore, constantly acting. This defect is obviated by the use of *convex* glasses, which render the pencils of light more convergent. Such glasses, are, of course, especially needed for near objects, as in reading, etc. They rest the eye by relieving the ciliary muscle from excessive work.

3. **Astigmatism.**—This defect, which was first discovered by Airy, is due to a greater curvature of the eye in one meridian than in others. The eye may be even myopic in one plane, and hypermetropic in others. Thus vertical and horizontal lines crossing each other cannot both be focussed at once; one set stands out clearly, and the others are blurred and indistinct. This defect, which is present in a slight degree in all eyes, is generally seated in the cornea, but occasionally in the lens as well; it may be corrected by the use of cylindrical glasses (*i.e.*, curved only in one direction).

4. **Spherical Aberration.**—The rays of a cone of light from an object situated at the side of the field of vision do not meet all in the same point, owing to their unequal refraction; for the refraction of the rays which pass through the edge of a lens is greater than that of those traversing its central portion. This defect is known as *spherical aberration*, and in the camera, telescope, microscope, and other optical instruments, it is remedied by the interposition of a screen with a circular aperture in the path of the rays of light, cutting off all the marginal rays, and only allowing the passage of those near the centre. Such correction is effected in the eye by the iris, which prevents the rays from passing through any part of the refractive apparatus but its centre. The image of an object will be most defined and distinct when the pupil is narrow, the object at the proper distance for vision, and the light abundant; so that, while a sufficient number of rays are admitted, the narrowness of the pupil may prevent the production of indistinctness of the image by *spherical aberration*.

Distinctness of vision is further secured by the pigment of the outer surface of the retina, the posterior surface of the iris and the ciliary processes, which absorbs most of the light which is reflected within the eye, and prevents its being thrown again upon the retina so as to interfere with the images there formed.

5. **Chromatic Aberration.**—In the passage of light through an ordinary convex lens, decomposition of each ray into its elementary colours commonly ensues, and a coloured margin appears around the image, owing to the unequal refraction which the elementary colours undergo. In optical instruments this, which is termed *chromatic aberration*, is corrected by the use of two or more lenses, differing in shape and density, the second of which continues or increases the refraction of the rays produced by the first, but by recombining the individual parts of each ray into its original white light, corrects any chromatic aberration which may have resulted from the first. It is probable that the unequal refractive power of the transparent media in front of the retina may be the means by which the eye is enabled to guard against the effect of chromatic aberration. The human eye is achromatic, however, only so long as the image is received at its focal distance upon the retina, or so long as the eye is properly accommodated. If these conditions are interfered with, a more or less distinct appearance of colours is produced.

From the insufficient adjustment of the image of a small white object, it appears surrounded by a sort of halo or fringe. This phenomenon is termed *Irradiation*. It is partly for this reason that a white square on a black ground appears larger than a black square of the same size on a white ground. The phenomenon is naturally more marked when the white object is a little out of focus.

6. **Defective Accommodation—Presbyopia.**—This condition is due to the gradual loss of the power of accommodation which is an early sign of advancing years. In consequence, the person is obliged in reading to hold the book farther and farther away in order to focus the letters, till at last the letters are held too far for distinct vision. The defect is remedied by weak convex glasses. It is due chiefly to the gradual increase in density of the lens, which is unable to swell out and become convex when near objects are looked at, and also to a weakening of the ciliary muscle, and a general loss of elasticity in the parts concerned in the mechanism. (Duke-Elder.)

Retinoscopy.

The refractive power of a lens is expressed in terms of its principal focal distance; if this is 1 metre, it is said to have the refractive power of 1 diopter (1 D.); a lens 2 D. has a focal length of

$\frac{1}{2}$ a metre, and a lens $\frac{1}{2}$ D. has a focal length of 2 metres, and so on. The lenses necessary for correcting errors of refraction in an eye are best determined by a simple instrument called a retinoscope; this is a small circular plane mirror, perforated by a hole in the centre through which the observer looks. If one reflects a spot of light from this on to a flat surface, any movement of the mirror produces a movement of the spot of light in the same direction; if the surface selected, however, is the eye of another person, the direction of movement of the illuminated spot on the retina may or may not be the same as that in which the mirror is moved, according to whether the observed eye is normal, hypermetropic, or myopic. If the observed eye is just a metre away from the observer, and is emmetropic, then as the mirror is tilted from side to side the spot moves in the same direction. If a convex lens is placed in a spectacle frame in front of the observed eye, the parallel rays which emerge from the retina are brought to a focus and cross before reaching the eye of the observer. Then the spot will move in the opposite direction to the mirror. A lens of less than 1 D. will not, however, accomplish this reversal; a lens of more than 1 D. will. So that a lens of 1 D. marks the exact point of reversal. If the observed eye is hypermetropic, the movement of the spot of light is also with the mirror, but stronger lenses than 1 D. must be introduced to get the point of reversal. If the lens in any particular case necessary for this purpose is 5 D., then the error of refraction is 4 D. and spectacles may be ordered accordingly*; for one always has to subtract 1 D., since that is required to get reversal with the normal eye.

When the spot of light moves against the mirror's movements from the first, then the observed eye is myopic, and the myopia is greater than 1 D. The "point of reversal" is determined by introducing concave lenses of increasing strength into the spectacle frame until the spot moves in the same direction as the mirror; the degree of myopia is equivalent to the value of the lens which accomplishes the reversal *plus* 1 D. to allow as before for the normal eye.

Many people have differences in the refractive error of their two eyes; so each should be tested separately. If the observed eye is astigmatic, the observations are more complicated, and must be made in the different meridians of the eye, and the point of reversal determined in each meridian by means of suitable cylindrical lenses

* The full correction often causes discomfort, and in practice is rarely ordered.

Functions of the Iris

The iris has the following two uses:—

1. To act as a diaphragm in order to lessen spherical aberration in the manner just described. This is specially necessary when one wishes to obtain a clearly defined image of an object; the pupil therefore contracts when accommodation for a near object takes place.

2. To regulate the amount of light entering the eye. In a bright light the pupil contracts; in a dim light it enlarges. This may be perfectly well seen in one's own iris by looking at it in a mirror in a poor light and then in a bright one.

The muscle-fibres (unstriated in mammals, striped in birds) of the iris are arranged circularly around the margin of the pupil, and radiatingly from its margin. The radiating fibres are best seen in the eyes of birds and otters; some look upon them as elastic in nature, but there is little doubt that they are contractile. Those who believe they are not contractile explain dilatation of the pupil as due to inhibition of the circular fibres. But if the iris is stimulated near its outer margin at three different points simultaneously the pupil assumes a triangular shape, the angles of the triangle corresponding to the points stimulated; this must be due to contraction of three strands of the radiating muscle; inhibition of the circular fibres would occur equally all round.

The iris is supplied by three sets of nerve-fibres contained in the ciliary nerves.

(a) The third nerve *via* the ciliary ganglion and short ciliary nerves supplies the circular fibres (fig. 276, p. 770).

(b) The cervical sympathetic supplies the radiating fibres. The cilio-spinal centre which governs them is in the cervical region of the cord. The fibres leave the cord by the anterior roots of the first and second thoracic nerve, pass into the cervical sympathetic, and reach the eyeball *via* the ophthalmic branch of the trigeminal, and long ciliary nerves (fig. 276).

(c) Fibres of the trigeminal nerve which are sensory.

Certain drugs dilate the pupil. These are called *mydriatics*; atropine is a well-known example. Others cause the pupil to contract. These are called *myotics*; physostigmine and opium (taken internally) are instances. Different drugs act in different ways, some exerting their activity on the muscular, others on the nervous structures of the iris, while some act centrally on the brain.

We may sum up the principal conditions under which the pupil contracts and dilates, in the following table:—

Causes of—

Contraction of the Pupil.

1. Stimulation of third nerve.
2. Paralysis of cervical sympathetic.
3. When the eye is exposed to light.
4. When accommodation occurs.
5. Under the local influence of physostigmine.
6. Under the influence of opium.
7. During sleep.
8. In chloroform anæsthesia in which a dilated pupil is a sign of danger.

Dilatation of the Pupil.

1. Paralysis of the third nerve.
2. Stimulation of the cervical sympathetic.
3. In the dark.
4. When the accommodation is relaxed.
5. Under the local influence of atropine. This drug also paralyzes the ciliary muscle.
6. In asphyxia. This is an important danger-signal in anæsthesia.
7. The injection of adrenaline.
8. Under the influence of certain emotions, such as fear.
9. During pain.
10. In ether anæsthesia.

There is a close connection of the centres that govern the activity of the two irides. If one eye is shaded by the hand, its pupil will of course dilate, but the pupil of the other eye will also dilate. The two pupils always contract or dilate together but may be prevented from doing so by local injury to the nerves of one side or the local action of drugs.

Functions of the Retina.

The retina is the nervous coat of the eye; it contains the layer of nerve-epithelium (rods and cones) which is capable of receiving the stimulus of light, and transforming it into a nervous impulse which passes to the brain by the optic nerve.

The layer of rods and cones is at the back of the other retinal layers, which the light has to penetrate before it can affect this layer. The proofs of the statement that this is the layer of the retina which is capable of stimulation by light are the following:—

(1) The point of exit of the optic nerve from the retina, where the rods and cones are absent, is insensitive to light, and is called the **blind spot**. This is readily demonstrated by what is known as Mariotte's experiment. If we direct one eye, the other being closed, upon a point at such a distance to the side of any object, that the image of the latter must fall upon the retina at the point of entrance of the optic nerve, this image is lost. If, for example, we

close the left eye, and look steadily with the right eye at the dot here represented, while the page is held about six inches from the



eye, both dot and cross are visible. On gradually increasing the distance between the page and the eye, still keeping the right eye steadily on the dot, it will be found that suddenly the cross disappears from view, because its image has fallen on the blind spot; on removing the book still farther, it comes in sight again. The question has arisen why we are not normally conscious of a gap in the image. We can only say that owing to the spot being blind from birth onwards we have come to neglect its blindness. The size of the blind spot at a given distance may be used to measure the optic disc (see p. 743).

(2) In the fovea centralis, in which the layers of the retina are thinned down to a minimum, light produces the greatest effect. In the macula lutea cones occur in large numbers, and in the fovea centralis cones without rods are found, whereas, in the rest of the retina which is not so sensitive to light, there are fewer cones than rods.

(3) If a small lighted candle is moved to and fro at the side of and close to one eye in a darkened room, while the eyes look steadily forward on to a dull background, branching *Purkinje's figures* are seen floating before the eye, consisting of dark lines on a reddish ground. As the candle moves, the figure moves in the opposite direction, and from its whole appearance there can be no doubt that it is a reversed picture of the retinal vessels projected before the eye.* This remarkable appearance is due to shadows of the retinal vessels cast by the candle; and it is only when they are thrown upon the retina in an unusual slanting direction that they are perceived. The branches of these vessels are distributed in the nerve-fibre and ganglionic layers; and since the light of the candle falls on the retinal vessels from in front, the shadow is cast behind them, and hence those elements of the retina which perceive the shadows must also lie behind the vessels. Here, then, we have a clear proof that the light-perceiving elements are not the inner, but one of the external layers of the retina; further than this, calculation has shown it is the layer of rods and cones. The data for such a calculation are—the dimensions of the eyeball, the distance of the screen from the eye, the angle through which the candle is moved, and the displacement of the figure seen.

The Function of the Rods and Cones.—The concentration of the

* Purkinje's figures can be more readily seen by simply looking steadily down a microscope, and moving the whole instrument backwards and forwards, or from side to side, while so doing.

cones in the macula immediately behind the centre of the pupil and the fact that each cone has a separate nerve-fibre indicate that the cones are concerned with acuity of vision.

The rods on the other hand are grouped together and are located more in the periphery. In birds which fly at night the cones are absent.

Changes in the Retina during Activity.

The method by which a ray of light is able to stimulate the endings of the optic nerve in the retina in such a manner that a visual sensation is perceived by the cerebrum is not yet understood. It is supposed that the change effected by the agency of the light which falls upon the retina is a physico-chemical alteration in the protoplasm, and that this change stimulates the optic nerve-endings. A certain temporary reddish-purple pigmentation (**visual purple**) is found in the outer limbs of the retinal rods in certain animals (*e.g.* frogs) which have been killed in the dark. The visual purple is bleached when the retina is exposed to light, and reappears when the light is removed, and it also undergoes distinct changes of colour when other than white light is used. If the operation is performed quickly enough, the bleached image of a bright object may be fixed on the retina by soaking the retina of an animal which has been killed in the dark, in alum solution.

The visual purple is derived in some way from the black pigment (melanin or fuscine) of the polygonal epithelium of the retina, since the colour is not renewed after bleaching if the retina is detached from its pigment layer.

Certain pigments, not sensitive to light, are contained in the inner segments of the cones. These are oil globules of various colours, red, green, and yellow, and are found in the retinae of marsupials (but not other mammals), birds, reptiles, and fishes. Nothing is known about the yellow pigment of the yellow spot.

In the lower vertebrates another change produced by the action of the light upon the retina is the **movement of the pigment cells**. On being stimulated by light the granules of pigment in the cells which overlie the outer part of the rod and cone layer of the retina pass into the processes of the cells, which hang down between the rods: these *melanin* or *fuscine* granules are generally rod-shaped, and look almost like crystals. A **movement of the cones** and possibly of the rods also occurs; in the light the cones shorten, and in the dark they lengthen (Engelmann). In mammals rapid changes in the size of the pupil appear to make this unnecessary.

Red light has no action on visual purple; the maximum bleaching effect takes place in greenish-yellow light. Now, when the living

eye is brought into a condition of "dark-adaptation," that is, when the retina has become adapted to light of low intensity, the colours of the spectrum alter in brightness; the red end becomes shortened and much darker; the blue end becomes brighter, and the region of maximum brightness is in the green. This change of brightness with change of adaptation, known as Purkinje's phenomenon, is absent in the fovea, where there are no rods. The selective action of the colours of the spectrum on the visual purple is so strikingly similar to the altered conditions of brightness just described that changes in the visual purple of the rods have been supposed to be the cause of sensations excited by feeble illumination (*i.e.* in the "dark-adapted" eye), while the cones are affected under more ordinary conditions of illumination. This conclusion gains support from several interesting facts. Visual purple is specially abundant in the retinae of almost all animals whose habits are nocturnal, or which live underground. Further, if the intensity of a colour stimulus is gradually increased, it is at first too faint to produce any sensation; then it produces a sensation of greyness, and at last the colour itself is seen; the interval between the appearance of the grey or white-black effect and of the true colour effect of the stimulus is spoken of as the "*photo-chromatic interval*." Red light has no effect on visual purple, and has no photo-chromatic interval (that is, it appears either red or nothing), and according to several observers, there is no such interval at the fovea, where the rods, and therefore visual purple, are absent. Thirdly, a very similar effect has been described by M'Dougall, when the retina is momentarily stimulated by a coloured light; the sensation arising from the stimulus is followed by a series of "primary responses" or after-sensations; the first members of the series have the same colour as the stimulus, and these are sometimes followed by a series of colourless (grey) sensations; these grey sensations are only present outside the fovea, and under conditions of "dark-adaptation" are absent with red and brightest with green stimuli. Here again we are able to differentiate between a visual-purple (rod) effect and a cone effect, the former, active under conditions of feeble illumination, affected most by green and unaffected by red light, and yielding colourless sensations; the latter being more specially concerned in developing sensations of colour under conditions of adaptation to ordinary light. The fovea centralis thus becomes the region where the colours of objects are best distinguishable, and where with ordinary illumination visual acuity is most marked. In the dark, however, extra-foveal (rod) vision is more sensitive than foveal (cone) vision; astronomers see faint stars more readily in the periphery of the field of vision. (See Hecht, 1937.)

Night Vision.—It has long been known that many persons suffer from varying degrees of inability to see, in a bad light, but the testing of soldiers for

night duties has indicated that minor degrees of the condition are much more common than hitherto imagined. It is of great practical importance in those who drive vehicles or pilot aircraft at night. A normal person ought to be fully dark-adapted in 30 minutes but after the age of thirty it takes longer. The Army has adopted an arbitrary standard of a large "V" mounted in five different positions on a translucent-screen behind which is a small lamp, the light from which can be varied. The subject is asked to write down the position of the V's which he is shown one by one. The night vision is recorded as $\frac{1}{2}$, $\frac{1}{3}$, $\frac{2}{3}$, etc., according to the number of V's seen. Night vision may also be recorded in terms of the minimum duration of a flash of light which the subject can perceive when dark adapted.

It has now become apparent that the condition is produced by lack of vitamin A. It is suggested that in the dark, vitamin A is transformed by combination with protein into visual purple and that light converts the visual yellow back into colourless substances and vitamin A. In night blindness benefit may accrue from the administration of this vitamin, but experience with night fighter pilots indicates that there is great individual variation, possibly dependent on hereditary factors in the power to see in a poor light.

Night blindness may also occur from slight degrees of oxygen want, such as prolonged flying at 10,000 feet. This may show itself by an apparent increase in the size of the blind spot, presumably because there is an area around it which is shaded from light by the radiating fibres of the optic nerve. Pilocarpine also has been found an effective drug in such cases, and this is also interesting because it hastens the regeneration of visual purple in the extirpated eye.

The electrical variations in the retina under the influence of light were discovered by Holmgren (1866), and since then have been investigated by M'Kendrick and Dewar, Einthoven, Waller, and others. The excised eyeball of a frog is led off by non-polarisable electrodes to a galvanometer. One electrode is placed on the front, the other on the back of the eye. If the eyeball is quite fresh, a current is observed passing through the eyeball from back to front. When light falls on the eye this current is increased; on shutting off the light there is a momentary further increase, and then the current slowly returns to its previous condition.

More recently the currents of action in the optic nerve of the eel (which is a conveniently long nerve) have been investigated by Adrian, who has found that the general laws applying to general sensation are applicable to the currents of action set up in the eye. The general law of Weber has been shown to apply, and adaptation occurs as in the nerve-endings concerned in pain.

The limits of visibility are 3300 A.U. in the violet and 8000 A.U. in the red.

Duration of Visual Sensations.—The duration of the sensation produced by a luminous impression on the retina is always greater than that of the impression which produces it. However brief the luminous impression, the effect on the retina always lasts for about one-eighth of a second. Thus, supposing an object in motion, say a horse, to be revealed on a dark night by a flash of lightning. The object would be seen apparently for an eighth of a second, but it would not appear in motion; because, although the image remained on the retina for this time, it was really revealed for such an extremely short period (a flash of lightning lasting only a millionth of a second) that no appreciable movement on the part of the object could have taken place in the period during which it was revealed to the retina of the observer. The same fact is proved in a reverse way. The spokes of a rapidly revolving wheel are not seen as distinct objects, because at every point of the field of vision over which the revolving spokes pass, a given impression has not

faded before another replaces it. Thus every part of the interior of the wheel appears occupied.

The stimuli which excite the retina are exceedingly slight; for instance, the minimum stimulus in the form of green light is equal in terms of work to that which is done in raising a ten-millionth part of a milligramme to the height of a millimetre, and even some of this is doubtless wasted in the form of heat. The time during which the stimulus acts may be excessively small; thus light from a rapidly rotating mirror is visible even when it only falls upon the retina for one eight-millionth part of a second. Some physiologists have drawn an analogy between retinal and muscular excitations. There is no complete analogy, but the following points of resemblance may be noted:—

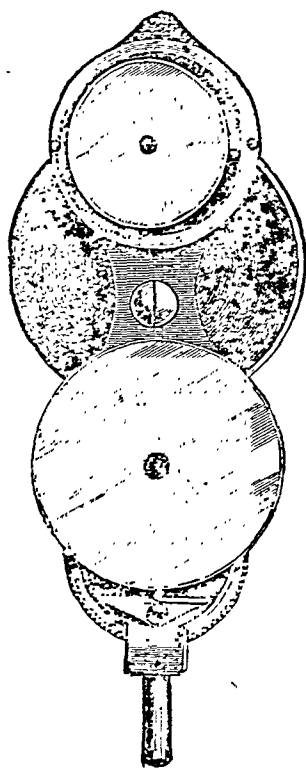


FIG. 269.—The ophthalmoscope. The small upper mirror is for direct, the larger for indirect, illumination.

1. The retina, like the muscle, possesses a store of potential energy, which the stimulus serves to fire off.

2. Fatigue on action and recovery after rest are noticeable in both.

3. The curve of retinal excitation, like the muscle curve, rises not abruptly but gradually to its full height, and on the cessation of the stimulus takes a measurable time to fall again, the retinal impression outlasting the stimulus by about one-eighth of a second.

4. With comparatively slow intermittent excitation, the phenomenon known as *flicker* takes place; this may be shown by the slow rotation on Maxwell's machine of a disc painted with alternate black and white sectors. This roughly corresponds with what in a muscle is called incomplete tetanus.

5. When the rate of stimulation is increased, as by increasing the speed of rotation of the disc just alluded to (say to twenty or thirty times a second) the resulting sensation is a smooth one of greyness. This fusion of individual stimuli into a continuous sensation does not by any means correspond to the complete tetanus of muscle, for the resultant sensation has a brightness corresponding not to a summation of the individual fusing sensations, but to a brightness which would ensue if the stimuli were spread evenly over the surface of the disc. (Talbot's Law.)

The Ophthalmoscope.

Everyone is perfectly familiar with the fact that it is quite impossible to see the *fundus* or back of another person's eye by simply looking into it. The interior of the eye forms a perfectly black background.* The same remark applies to the

* In some animals (e.g. the cat), the pigment is absent from a portion of the retinal epithelium; this forms the *Tapetum lucidum*. The use of this is supposed to be to increase the sensitiveness of the retina, the light being reflected back through the layer of rods and cones. It is probably the case that these animals are able to see clearly with less light than we can, hence the popular idea that a cat can see in the dark. In fishes a tapetum lucidum is often present; here the brightness is increased by crystals of guanine.

difficulty we experience in seeing into a room from the street through the window unless the room is lighted within. In the eye this fact is partly due to the feebleness of the light reflected from the retina, most of it being absorbed by the retinal pigment; but far more to the fact that every such ray is reflected straight to the source of light (*e.g.* candle), and cannot, therefore, be seen by the unaided eye without intercepting the incident light from the candle as well as the reflected rays from the retina. This difficulty is surmounted by the use of the *ophthalmoscope*.

The ophthalmoscope was invented by Wharton Jones, forgotten, then reinvented by Helmholtz; as a mirror for reflecting the light into the eye, he employed a bundle of thin glass plates; this mirror was transparent, and so he was able to look through it in the same direction as that of the rays of the light it reflected.

In its most modern form a concave mirror is mounted on a handle, and is perforated in the centre by a small hole through which the observer can look while the light is supplied from a small electric bulb in the handle of the instrument.

The methods of examining the eye with this instrument are—the *direct* and the *indirect*: both methods of investigation should be employed. A drop of a solution of atropine sulphate (two per cent.) or of homatropine hydrobromide should be instilled about twenty minutes before the examination is commenced; the ciliary muscle is thereby paralysed, the power of accommodation is abolished, and the pupil is dilated. This will materially facilitate the examination; but it is quite possible to observe all the details to be presently described without the use of such drugs. The room being now darkened, the observer seats himself in front of the person whose eye he is about to examine, placing himself upon a somewhat higher level. Let us suppose that the right eye of the patient is being examined. If the instrument is not supplied with an electric light, a brilliant and steady light is placed close to the left ear of the patient.

Direct method.—Taking the small mirror in his right hand, and looking through the central hole, the operator directs a beam of light into the eye of the patient. A red glare is seen, due to the illumination of the retina. The patient is then told to look at the little finger of the observer's right hand as he holds the mirror; to effect this the eye is rotated somewhat inwards, and at the same time the retina changes from red to a lighter colour, owing to the reflection from the optic disc. The observer now approximates the mirror, with his eye to the eye of the patient, taking care to keep the light fixed upon the pupil so as not to lose the reflex. At a certain point, which varies with different eyes, but is usually reached when there is an interval of about two or three inches between the observed and the observing eye, the vessels of the retina become visible. Examine carefully the fundus of the eye, *i.e.*, the red surface—until the optic disc is seen; trace its circular outline, and observe the small central white spot, the *porus opticus*, or *physiological pit*: near the centre is the central artery of the retina breaking up upon the disc into branches; veins also are present, and correspond roughly to the course of the arteries. Trace the vessels over the disc on to the retina. Somewhat to the outer side, and only visible after some practice, is the *macula* or *yellow spot*, which appears red with the ophthalmoscope, with the smaller lighter-coloured *fovea centralis* in its centre. This constitutes the direct method of examination; by it the various details of the fundus are seen as they really exist, and it is this method which should be adopted for ordinary use (fig. 270).

If the observer is myopic or hypermetropic, he will be unable to employ the

direct method of examination until he has remedied his defective vision by the use of proper glasses.

In the indirect method the patient is placed as before, and the operator holds the large mirror in his right hand at a distance of twelve to eighteen inches from the patient's right eye. At the same time he rests his left little finger lightly upon the patient's right temple, and holding a convex lens between his thumb and forefinger, two or three inches in front of the patient's eye, directs the light through the lens

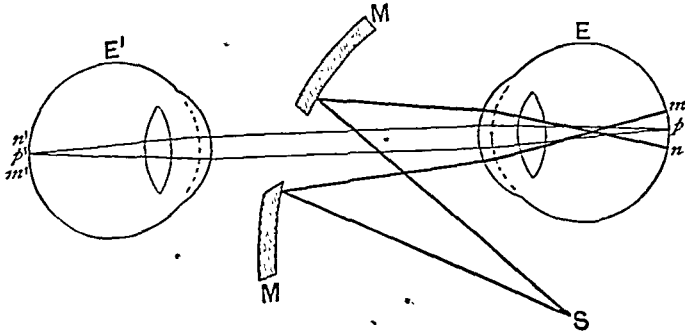


FIG. 271.—The course of the light in examining the eye by the direct method. (T. G. Brodie.)

into the eye. The red reflex, and subsequently the white one, having been gained, the operator slowly moves his mirror, and with it his eye, towards or away from the face of the patient, until the outline of one of the retinal vessels becomes visible, when very slight movements on the part of the operator will suffice to bring into view the details of the fundus above described; more of the retina is seen at a time, but the image will be much smaller and inverted. The appearances seen are depicted in fig. 270. The lens should be kept fixed at a distance of two or three inches, the mirror alone being moved until the disc becomes visible: should the image of the mirror, however, obscure the disc, the lens may be slightly tilted.

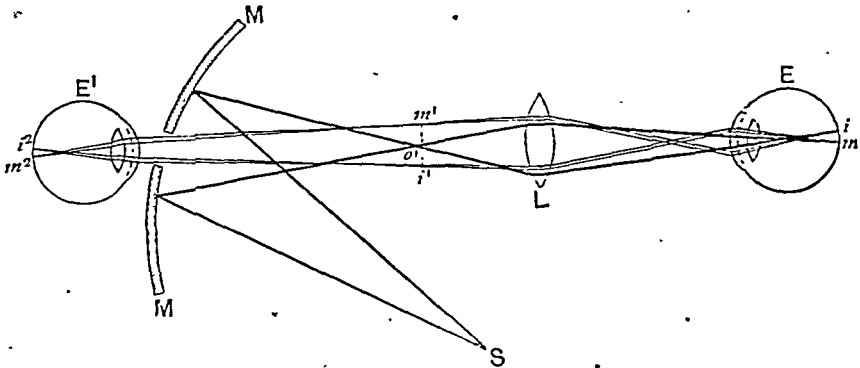


FIG. 272.—The course of the light in examining the eye by the indirect method. (T. G. Brodie.)

Figures 271 and 272 show diagrammatically the course of the rays of light.

Fig. 271 represents what occurs when employing the direct method. S is the source of light, and M M the concave mirror with its central aperture, which reflects the rays; these are focussed by the eye E, which is being examined, to a point in the vitreous humour, and this produces a diffuse lighting of the interior of the eyeball. Rays of light issuing from the point p emerge from the eye parallel to one another, and enter the observer's eye E'; they are brought to a focus p' on the retina as the eye is accommodated for distant vision. Similarly the point m and n will give rise to images at m' and n' respectively.

Fig. 272 represents what occurs in examining the eye by the indirect method.

S is the source of light, M M the mirror, E the observed, and E^1 the observing eye as before. The rays of light are reflected from the mirror and form an image at o^1 ; they then diverge and are again made convergent by the lens L held in front of the eye by the observer; by this means a second image is focussed just behind the crystalline lens of the eye E. They then again diverge and diffusely light up the interior of the eyeball. The rays of light reflected from two points i and m on the retina diverging from the eye are refracted by the glass lens L, and give an inverted real image $i^1 m^1$ larger than the object $i m$. These latter rays then diverge, and are collected and focussed by the observing eye E^1 to give an image $i^2 m^2$ on the retina.

The Perimeter.

This is an instrument for mapping out the field of vision. It consists of a graduated arc, which can be moved into any position,

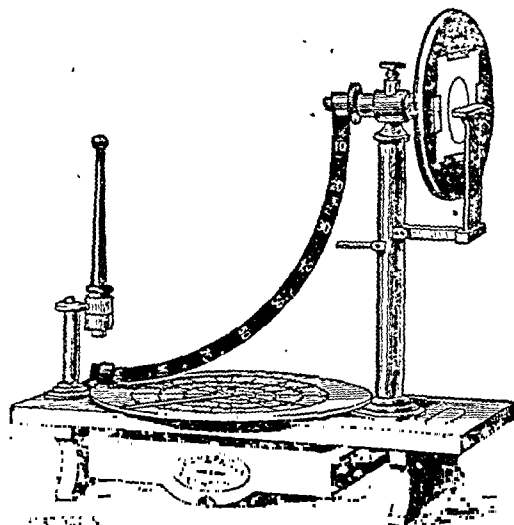


FIG. 273.—Priestley Smith's perimeter.

and which when rotated traces out a hollow hemisphere. In the centre of this the eye under examination is placed, the other eye being closed. The examiner then determines on the surface of the hemisphere those points at which the patient just ceases or just begins to see a small object moved along the arc of the circle. These points are plotted out on a chart graduated in degrees, and by connecting them the outline of the field of vision is obtained.

Fig. 273 shows one of the forms of perimeter very generally employed, and fig. 274 represents one of the charts provided with the instrument.* The dark line represents the normal average field of vision for the right eye. It will be seen that the field of vision is most extensive on the outer side; it is less on the inner side because of the presence of the nose. Considerable personal variation occurs. The blind spot may also be mapped out.

* By the use of illuminated objects in a dark room still more detail may be obtained and even the paths of the retinal arteries made out. (Livingston.)

By the use of the same instrument, it is found that the colour of a coloured object is not distinguishable at the margin, but only towards the centre of the field of vision, but there are differences for different colours; thus a blue or yellow object is seen to be blue or yellow over a wider field than a red or green one.

In disease of the optic nerve, contraction of the field of vision for white and coloured objects is found. This often occurs before any change in the optic nerve is discoverable by the ophthalmoscope.

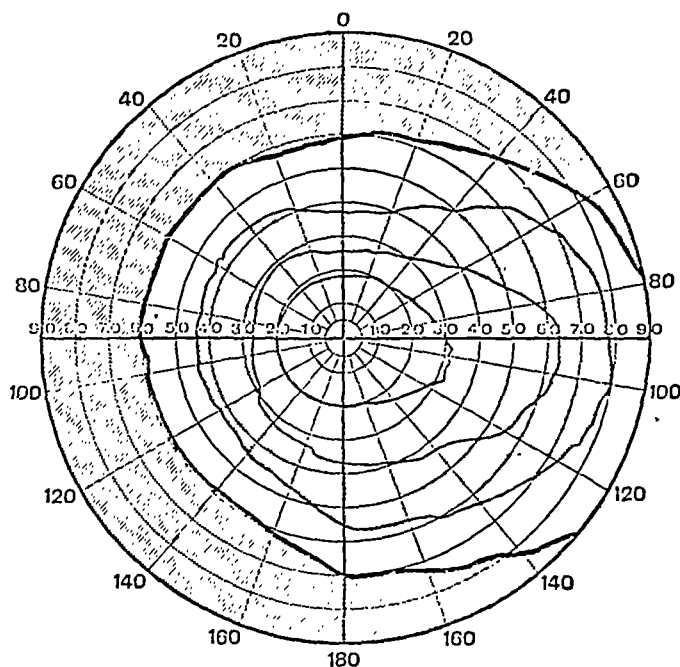


Fig. 274.—Perimeter chart showing average fields of vision for white and three colours. The outer limit of the colours is shown, but they all overlap towards the centre. The dark area is caused by the nose, etc.

The yellow spot of one's own eye can be rendered evident by what is called Clerk-Maxwell's experiment:—On looking through a solution of chrome-alum in a bottle with parallel sides, an oval purplish spot is seen in the green colour of the alum. This is due to the pigment of the yellow spot.

Visual Sensations.

Visual sensations are of two kinds, colour sensations and colourless sensations. Colour sensations differ (1) in *hue*, for instance, blue, red, yellow; (2) in *saturation*, for instance, pale green and full green; this depends upon the degree of admixture with white light; and (3) in *intensity*, for instance, a weak sensation or a strong sensation. These differences are in part dependent respectively on the length,

the purity, and the amplitude of the light-wave; but they are also dependent on the local or general condition of the cerebro-retinal apparatus at the time of stimulation. Colours also differ (4) in *brightness* or *luminosity*; this is a purely psychological quality devoid of any known physical counterpart. The brightness of a colour may be measured by determining the shade of grey to which it appears equivalent. Even the most saturated colours (for instance, yellow and blue) have different degrees of brightness.

Colourless sensations include the grey series from the deepest black to the most blinding white.

If a ray of sunlight is allowed to pass through a prism, it is decomposed by its passage into rays of different colours, which are called the colours of the spectrum; they are red, orange, yellow, green, blue, indigo, and violet. The red rays are the least turned out of their course by the prism, and the violet the most, whilst the other colours occupy in order places between these two extremes. The differences in the colour of the rays depend upon the rapidity of vibrations producing each, the red rays being the least rapid and the violet the most. In addition to these, there are other rays which are invisible but which have definite properties; those to the left of the red are less refrangible, being the infra-red or calorific rays which act upon the thermometer, while those to the right of the violet, which are called the actinic or ultra-violet rays, have a powerful chemical action.

White light may be built from its constituents in several ways, for instance, by a second prism reversing the dispersion produced by the first, or by causing the colours of the spectrum to fall on the retina in rapid succession. The best way to study the effects of compounding successive colour stimuli is by means of a rapidly revolving disc to which two or more coloured sectors are fixed. Each colour is viewed in rapid succession, but owing to the persistence of retinal impressions, the constituent colour stimuli give a single sensation of colour.

A colourless sensation can be produced by the mixture of three colours, or even of two colours in certain hues and proportions. These pairs of colours, of which red and greenish-blue, orange and blue, and violet and yellow are examples, are called *complementary*.

Thus blue and orange, when rotated on the colour-wheel, produce a colourless sensation; but it is well known that a mixture of blue and orange paint gives green. This is explained on the supposition that the colours used are not pure and that each contains green; the true blue and orange present neutralise each other to produce white, and thus green is the only colour sensation obtained.

Colour Vision.

All visual sensations show the usual peculiarities of sensations, that is, they possess differences in quality, in intensity and in position. The intensity factor is related to the frequency of impulses up the optic nerve. The position depends upon the pattern formed on the retina and on stereoscopic vision. The quality remains to be considered.

The visual sensations can be analysed psychologically into six distinct ones, namely, white, black, blue, green, yellow and red. This means that we cannot recognise any mixture in these sensations, but we can analyse other colours into them, *e.g.*, blue-green is a combination of blue with green.

The physical cause of visual sensations consists of radiations of certain wave-lengths forming the visible spectrum or light. Certain sensations cannot be produced by any single part of the spectrum.

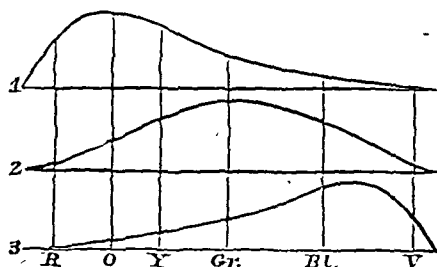


FIG. 275.—Diagram of the three primary colour sensations. (Young-Helmholtz theory.) 1 is the red; 2, green, and 3, violet primary colour-sensation. The lettering indicates the colours of the spectrum. The diagram indicates by the height of the curve to what extent the several primary sensations of colour are excited by vibrations of different wave-lengths.

The sensation of black is produced by a *relative* deficiency of stimulation and the sensation of white can be aroused by selected stimuli from two or more parts of the spectrum up to the whole of the spectrum of selected light sources. Thus we see that a unitary sensation is not necessarily related to a homogeneous stimulation.

With the exception of black and shades of colours with it all colour sensations can be aroused by using mixtures obtained from three selected regions of the spectrum and the ones selected are usually red, green and blue (or violet). This fundamental relationship led Young to suggest that there were three sets of nerve fibres, one set for each of the three selected colour sensations. This trichromatic theory was elaborated by Helmholtz who added the idea that there were three photosensitive substances in the retina which were acted upon to different degrees by the various parts of the spectrum. Up to the present only one photosensitive substance

(visual purple) has been demonstrated, and it is acted upon by the whole of the visible spectrum in a comparable degree to the sensitivity of the eye to light.

A rival theory proposed by Hering is based on psychological considerations. It can be disproved in relation to the sensation of yellow. According to Hering's hypothesis the yellow sensation is due to a cancelling of photo-chemical effect when stimuli corresponding to red and to green are balanced on the retina. As a sensation of yellow can be produced by binocular fusion in which one eye is stimulated to give a red sensation and the other to give a green one, this balancing cannot be in the retina but beyond the optic chiasma.

The Young-Helmholtz hypothesis described earlier is not satisfactory in explaining red-green confusion. At present the only modification of Young's hypothesis which, according to Roaf, seems most satisfactory is based on the presence of coloured globules in the retinae of amphibians, reptiles, birds and marsupials. Each of these globules is in front of a cone so that that cone can be stimulated only by that portion of the spectrum which passed through the coloured globule. Unfortunately, these globules have never been described in the retina of mammals. On the other hand, many mammals may have defective colour vision. (See Roaf.)

Defective Colour Vision.—Defective colour vision may be due to disease of the eye, but the commonest form is congenital. The defect in the usual type is a failure to distinguish the parts of the spectrum in the region which gives rise to the sensation of yellow. A common defect is a failure to distinguish red from green, but different types of defective colour vision are seen (see Plate facing p. 766).

C. J. Burch found that by exposing the eye to bright sunlight in the focus of a burning-glass behind transparent coloured screens, it is possible to produce temporary colour-blindness. After red light, the observer is for some minutes red-blind, scarlet geraniums look black, yellow flowers green, and purple flowers violet. After violet light, violet looks black, purple flowers crimson, and green foliage richer than usual. After light of other colours, corresponding effects are produced. If one eye is made purple-blind, and the other green-blind, all objects are seen in their natural colours, but in exaggerated perspective, due to the difficulty the brain experiences in combining the images from the two eyes.

By using a brightly illuminated spectrum, and directing the eye to certain of its colours, the eye in time becomes fatigued and blind for that colour, so that it is no longer seen in the spectrum. Thus, after green blindness is induced, the red appears to meet the blue, and no green is seen. If, however, the eye is exposed to yellow light, it does not similarly become blind for yellow only, but for red and green too. This supports the Young-Helmholtz theory, that the sensation yellow is one compounded of the red and green sensations. By an exhaustive examination of the different parts of the spectrum in this way it thus becomes possible to differentiate between the primary colour sensations and those which are compound. By a study of this kind, Burch concluded that the phenomena of colour vision are in accordance with the Young-Helmholtz theory, with the important addition that

there is a fourth primary colour sensation, namely, blue. He could not discover that colour sensations are related to each other in the sense indicated by Hering. Each may be exhausted without either weakening or strengthening the others. These observations were confirmed by examining in a similar way the colour sensations of seventy other people, but there are individual differences in the extent to which the colour sensations overlap.

Edridge-Green aims at describing facts rather than theories. Normal people are hexachromatic, *i.e.*, they can name six colours (and eighteen shades) in the spectrum; a few people are more expert and can see a seventh colour—indigo between blue and violet, and can distinguish more shades. Colour-blind people may be (a) those who can see the whole spectrum and cannot distinguish its colours; some can see only two colours in it; (b) those who cannot see either the red or the violet end, but can nevertheless discriminate the colours in the parts that are visible; and (c) those who combine both defects. There may be all grades of these defects. The colour-blind person is usually a dichromic and can distinguish only the two ends of the spectrum as different colours; if this is combined with a shortening of the red end, the defect is more pronounced and more dangerous; others are trichromic and can distinguish red, green, and violet; between this and the normal there may also be tetra- and pentachromic people.

How subjects suffering from defective colour vision may view the same object is shown by the Edridge-Green parrots (facing).

Tests for Colour-Blindness.—This red-green confusion is of practical importance as coloured signals must be recognised by railway and marine employees, and to a certain extent by motor drivers.

The most practical test is the use of a lantern showing coloured lights, the importance of which was demonstrated by Edridge-Green.

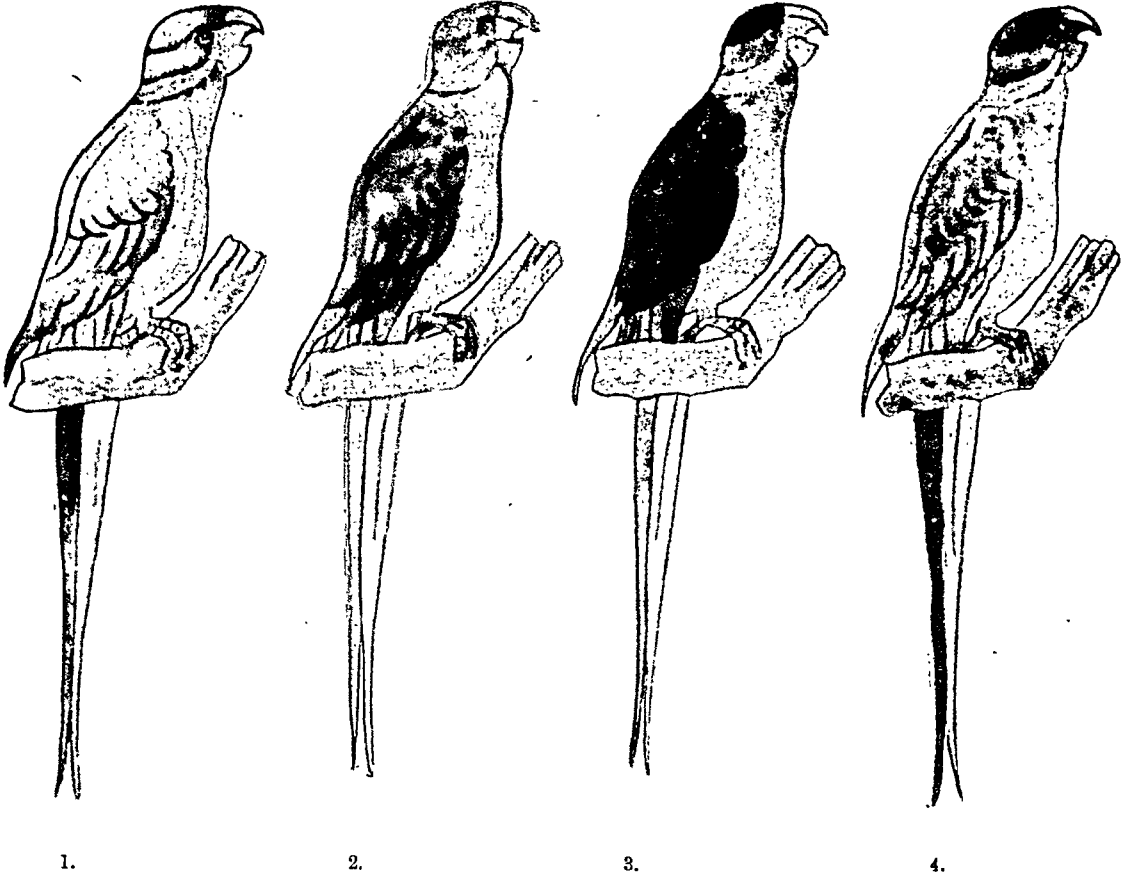
As colour recognition depends upon the intensity, area stimulated and duration of exposure, these factors should be considered, and for proper testing small apertures at a suitable distance must be employed. Matching colours as in Holmgren's wool test is not satisfactory, as the texture, luminosity, etc., furnish ancillary means of distinguishing one object from the other. If such tests are employed the materials should be of wool, silk, etc., mixed so that the surface reflexions will confuse the examinee.

A very simple and reliable method is to use pseudo-isochromatic plates, that is, figures on which numbers or letters can be detected by differences in colour, but the colours are so chosen that the person with defective colour vision fails to see the pattern recognised by the normal person but may see quite a different outline. The best of these is that of Edridge-Green, in which the colours are formed of spots which differ in size and purity as well as in hue, so that the recognition of the object can be only by the difference in hue.

A number of similar card tests, notably those of Ishihara, have been introduced, but are not so satisfactory for testing all varieties of colour blindness.

After-Images.—These are the after-effects of retinal excitation, and are divided into *positive* and *negative*. Positive after-images

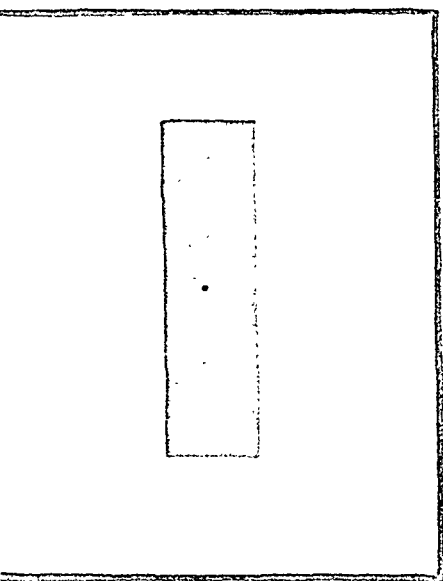
THE EDRIDGE GREEN PARROTS



1. A parrot as coloured by a normal person.
- 2 and 3 are illustrations of the same parrot coloured by men who saw only two colours. In 2, the green wings have become brownish-red and the red part of the tail feathers green. In 3, there are no reds. Both men would confuse traffic signals.
- In 4, the artist had three-colour vision—he saw only red, green and violet. He saw yellow as red when it was next to green, but saw it as green when it was next to red.



FIG. 270.—Normal fundus of average tint. Reproduced by permission from the original drawing in May and Worth's *Diseases of the Eye* (Baillière, Tindall & Cox).



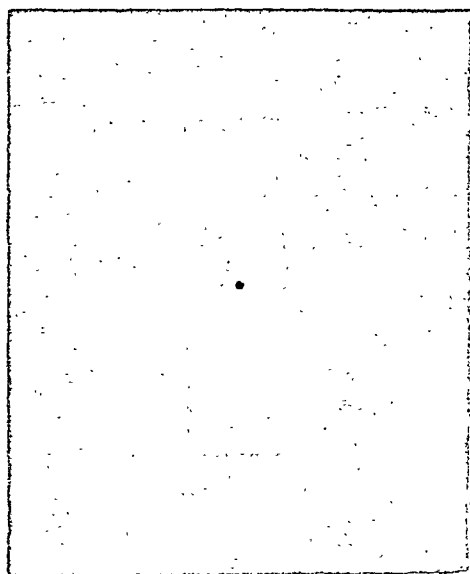
I.



II.



III.



IV.

Plate to illustrate simultaneous and successive contrast.

For explanation see text.

[Face page 766.]

resemble the original image in distribution of brightness and colour. In negative after-images bright parts appear dark, dark parts bright, and coloured parts in the complementary colours.

If a bright white object is looked at, and the eyelids are then closed, a positive after-image is seen which fades gradually, but as it fades it passes through blue, violet, or red to orange; according to the Young-Helmholtz theory, this is explained on the hypothesis that the excitation does not decline with equal rapidity in the three colour terminals. A positive after-image is readily obtained by momentarily looking at a bright object, *e.g.* a window, after waking from sleep. Negative after-images may be seen either by closing the eyes or by turning them to a uniform grey surface after viewing an object steadily. If the object looked at is coloured, the negative after-image seen upon such a background is in its complementary colour; this is explained by the Young-Helmholtz theory, on the supposition that the colour-perceiving element for the colour looked at is the most fatigued, and the terminals for its complementary colour least fatigued. On the Hering theory, one colour produces anabolic or katabolic effects as the case may be; on withdrawing the eye from stimulation by that particular colour, the opposite phase of metabolism takes place and produces the complementary colour.

Simultaneous and Successive Contrast.—Negative after-images are frequently spoken of as phenomena of *successive contrast*. The phenomena of *simultaneous contrast* are well illustrated by the four figures of the accompanying Plate. In all these figures the oblong grey strip is actually of the same brightness. This can easily be proved by screening from view the surrounding parts of the figures, which cause the greys to appear different. The grey in I appears darker than that in II, while the grey in III appears yellowish, and in IV reddish. If these effects are not sufficiently obvious, they immediately become so when the entire surface is covered over with a sheet of thin tissue paper.

Figs. I and II are examples of *brightness contrast*; Figs. III and IV of *colour contrast*. The effects of these two varieties of simultaneous contrast may be stated thus: a given grey object looks darker when viewed against a bright background than when viewed against a dark background; when the background is coloured, it is tinged with the complementary colour of the former.

Helmholtz attributed the effects of simultaneous contrast to errors of judgment, and not to altered conditions of the retinal apparatus.* But there can be no doubt that simultaneous contrast has as simple a sensory origin as successive contrast (negative after-

* By "retina" here and elsewhere we mean "cerebro-retinal apparatus." We have no knowledge of the precise share of retina and brain in the development of visual sensations and after-sensations.

images). For if either of the two lower figures of the Plate is carefully fixated for about a minute (fixation of the central dot will help to prevent involuntary movements of the eyes), and if the gaze is then transferred to a spot on a sheet of white or grey paper, not only will the outer squares appear in their complementary colour, but also the grey strips will appear tinged, now likewise in a complementary colour. So, too, if a point midway between Figs. I and II is fixated, and the Plate held at a sufficient distance for both figures to be simultaneously visible, the after-image of the grey strip of II will appear darker than that of I.

Seeing that simultaneous contrast persists in after-images, and seeing how generally recognised are its effects (for instance, by the painter, who depicts in *blue* the shadows cast by an object on the yellow sand), it seems far more probable that the part played by the higher mental processes consists, not, as Helmholtz supposed, in causing the illusion, but in reducing or overcoming it. According to this view, experience educates us to see objects in what we know to be their real colour, instead of in the colour which would result from the operation of simultaneous contrast. Some support is lent to this view by the fact that contrast is much enhanced when all irregularities are, as far as possible, eliminated from the surface of the object (here, the grey oblong) in which the contrast colour is induced, or when that object is made to appear, *e.g.* by covering the whole with tissue paper, to combine with the object (the coloured square) which induces the contrast colour, so as to form an apparently single object. On the other hand, colour contrast is very markedly reduced, if the grey object is outlined in pencil on the tissue paper through which it is viewed. Thus, whatever tends to the apparent independence of the object in which the contrasting colour is induced tends to the reduction of the contrast effect.

Insisting on the sensory nature of simultaneous contrast, Hering explained it in the following way. He supposed that excitation of an area of the retina by a stimulus of given colour or brightness simultaneously induces an opposite metabolic process in the same colour apparatus in neighbouring areas of the retina. When, for example, a part of the retina is being stimulated by blue, the anabolic change thus evoked in the yellow-blue apparatus simultaneously is supposed to induce a katabolic change in the same apparatus in the neighbouring retinal area which is being excited by a grey stimulus. Consequently, the grey acquires a yellowish tinge.

Binocular Colour-mixture.—By means of the stereoscope, binocular combinations of colour can be obtained. Thus, if one eye is exposed to a red disc, and the corresponding portion of the other eye to a yellow one, the mind usually perceives one disc of an orange tint; but frequently, especially if there be differences of brightness or of

form in the two objects, we notice that "rivalry of the fields of vision" occurs, first one then the other disc rising into consciousness. A stereoscopic combination of black and white produces the appearance of metallic lustre; this is very beautifully shown with figures of crystals, one black on a white ground, the other white on a black ground. The combination of black and white is interpreted as indicating a polished surface, because a polished surface reflects rays irregularly, so that the two eyes receive stimuli of unequal intensity.

REFERENCE.—Roaf.

Nervous Paths connected with Vision.

The correspondence of the two retinæ and of the movements of the eyeballs is produced by a close connection of the nervous centres controlling these phenomena, and by the arrangement of the nerve-fibres in the optic nerves. The crossing of the nerve-fibres at the optic chiasma is incomplete, and the next diagram (fig. 276) gives a simple idea of the way the fibres go.

It will be seen that it is only the fibres from the inner portions of the retinæ that cross; and that those represented by shaded paths from the right side of the two retinæ ultimately reach the right hemisphere, and those represented by darker lines from the left side of the two retinæ ultimately reach the occipital cortex left hemisphere. The two halves of the retinæ are not, however, separated by a hard-and-fast line from one another; the two halves slightly overlap, which means the central region of each retina is represented in each hemisphere. It has been found that the macula is represented by a relatively large area on the cortex.

By studying the action potentials set up in the occipital cortex when narrow beams of light are shone upon the different parts of the retina, it has been found that each part has a spatial representation in the cortex; that is to say, a beam of light of a certain shape would set up impulses in an area of a similar shape on the cortex. See also "The Sensory Areas of the Cerebral Cortex," p. 639.

Fig. 276, though diagrammatic, will assist the reader in more fully comprehending the paths of visual impulses, and the central connections of the nerves and nerve-centres concerned in the process. The fibres from the retina to the external geniculate body end there by arborising round its cells, and a fresh relay of fibres from these cells passes in the posterior part of the internal capsule to the cortex of the occipital lobe. Those to the superior corpus quadrigeminum are continued by a fresh relay to the nuclei of the

nerves concerned in eye-movements (represented by the oculo-motor nucleus in the diagram); the axons of the cortical cells pass to the

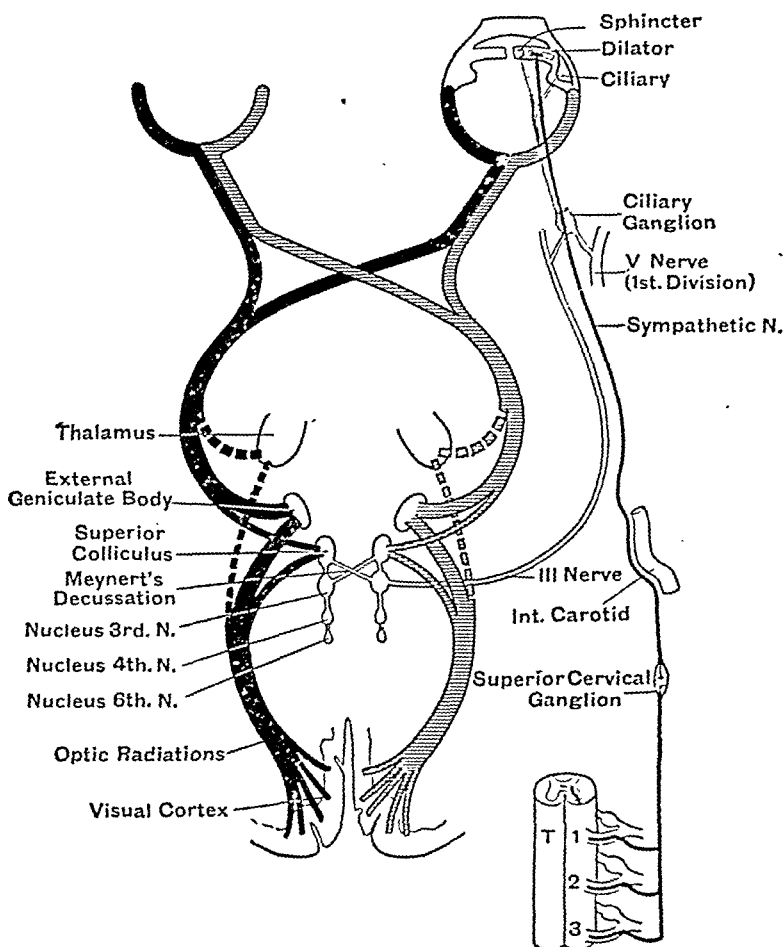


FIG. 276.—Diagram to show the paths of the nervous impulses concerned in sight, also those connected with the innervation of the pupil. (From McDowall's *The Science of Signs and Symptoms*.)

tegmentum, whence a fresh relay continues the impulse to the oculo-motor nucleus.

The Reflexes of the Eye.

The reflexes in the region of the eye are not only of physiological interest, but not infrequently of valuable diagnostic significance.

The Conjunctival Reflex.—This reflex is designed to protect the cornea from injury, and has for its afferent path the fifth nerve and its endings in the conjunctiva. When this path is stimulated the impulse passes backwards to the Gasserian ganglion, and thence *via* the pons to the oculo-motor nerve, which brings about closure

of the eyelid. If the stimulation is sufficiently severe, the nucleus of the seventh nerve is also stimulated, producing constriction of the orbicularis palpebrarum.

Reflex closure also occurs if a blow is seen coming towards the eye, but in this instance the path must depend on association fibres between the optic tract with which the optic nerve is continuous and the nuclei of the third and seventh nerves.

The Light Reflex.—By the light reflex the retina is protected from an excessive or dangerous amount of light. It is a true reflex, the afferent path being the optic nerve and tract to the superior colliculus and to the pretectal transitional area between the thalamus and mid-brain where they synapse. Some second neurones (Meynert's fibres) cross in the posterior commissure to reach the Edinger-Westphal division of the nucleus of the third nerve and some go direct (see fig. 276). It seems likely from the action of atropine, that the fibres of the third nerve which supply the iris sphincter are really parasympathetic in nature, although they have their origin in close association with the nucleus of the third nerve in the floor of the aqueduct of Sylvius. Atropine is known to paralyse all parasympathetic activity.

It is important to remember the bilateral nature of the stimulus in any attempt to elicit the reflex. The stimulus for each pupil arises from half the retina of both sides. To obtain the reaction, both eyes must be shaded and one suddenly uncovered, when, if the patient has been asked to look towards the light, the pupil is seen to contract.

In tabes, and general paralysis, the absence of the light reflex with the retention of the reaction to accommodation—the so-called Argyll-Robertson pupil—is often obtained. It will be seen from fig. 276 that such a condition can be brought about by degeneration of Meynert's fibres which cuts off the efferent from the afferent neurone in the light reflex. It is clear from the figure that it is necessary to keep the eye not under investigation covered, for the third nerve nucleus may be influenced by impulses reaching it from both eyes.

The Reaction to Accommodation, although strictly speaking not a reflex, is commonly investigated with the reflexes of the eye. It is really a motor movement associated with convergence, and designed to cut off those parts of the field of vision less accurately focussed. More detailed images are produced by focussing on the macula which is straight behind the centre of the pupil. As the mechanism of accommodation is so closely related to that of refraction, it has been considered in relation to "Vision."

Visual Judgments.

The psychical or mental processes which constitute the visual sensation proper have been studied to a far greater degree than is possible in connection with other forms of sensation.

We have already seen that in spite of the inversion of the image in the retina, the mind sees objects in their proper position (see p. 743).

We are also not conscious of the blind spot. This is partly due to the fact that those images which fall on the blind spot of one eye are not focussed there in the other eye. But even when one looks at objects with one eye, there is no blank, for the reason explained on p. 754.

Our estimate of the size of various objects is based partly on the visual angle (p. 742) which they subtend, but much more on the estimate we form of their distance. Thus a lofty mountain many

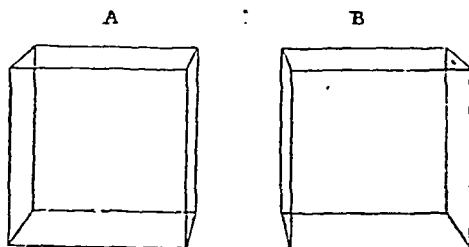


FIG. 277.—Diagrams to illustrate how a judgment of a figure of three dimensions is obtained.

miles off may be seen under the same visual angle as a small hill near at hand, but we infer that the former is much the larger object because we know it is much farther off than the hill. Our estimate of distance is, however, often erroneous, and consequently the estimate of size also. Thus persons seen walking on the top of a small hill against a clear twilight sky appear unusually large, because we overestimate their distance, and for similar reasons most objects in a fog appear immensely magnified.

The action of the sense of vision in relation to external objects is, therefore, quite different from that of the sense of touch. The objects of the latter sense are immediately present to it; and our own body, with which they come in contact, is the measure of their size. The part of a table touched by the hand appears as large as the part of the hand receiving an impression from it, for the part of our body in which a sensation is excited is here the measure by which we judge of the magnitude of the object. In the sense of vision, on the contrary, the images of objects are mere fractions of the objects themselves, realised upon the retina, the extent of which remains constantly the same. But the mind, into which the sensations of vision are incorporated, invests the images of objects,

together with the whole field of vision in the retina, with very varying dimensions; the relative size of the image in proportion to the whole field of vision, or of the affected parts of the retina to the whole retina, alone remains unaltered.

The estimation of the form of bodies by sight is the result partly of the mere sensation, and partly of the association of ideas. Since the form of the images perceived by the retina depends wholly on the outline of the part of the retina affected, the sensation alone is adequate to the distinction of superficial forms from each other, as of a square from a circle. But the idea of a solid body, such as a sphere, or a cube, can only be attained by the action of the mind constructing it from the different superficial images seen in different positions of the eye with regard to the object, and, as shown by Wheatstone and illustrated in the *stereoscope*, from two different perspective projections of the object being presented simultaneously to the mind by the two eyes.

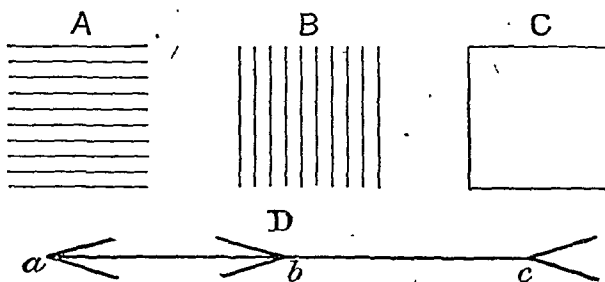


FIG. 278.—Diagrams to illustrate visual illusions.

Thus, if a cube is held at a moderate distance before the eyes, and viewed with each eye successively while the head is kept perfectly steady, A (fig. 277) will be the picture presented to the right eye, and B that seen by the left eye. Wheatstone has shown that on this circumstance depends in a great measure our conviction of the solidity of an object, or of its projection in relief. If different perspective drawings of a solid body, one representing the image seen by the right eye, the other that seen by the left (for example, the drawings of a cube, A, B, fig. 277), are presented to corresponding parts of the two retinae, as may be readily done by means of the stereoscope, the mind will perceive not merely a single representation of the object, but a body projecting in relief, the exact counterpart of that from which the drawings were made.

By transposing two stereoscopic pictures a reverse effect is produced; the elevated parts appear to be depressed, and *vice versa*. An instrument contrived with this purpose is termed a *pseudoscope*. Viewed with this instrument a bust appears as a hollow mask, and as may readily be imagined the effect is most bewildering.

The clearness with which the details of an object are perceived,

irrespective of accommodation, would appear to depend largely on the number of rods and cones which its retinal image covers. Hence the nearer an object is to the eye (within moderate limits) the more clearly are all its details seen. Further, if we want carefully to examine any object, we always direct the eyes straight to it, so that its image shall fall on the two maculæ, where an image of a given area will cover a larger number of cones than anywhere else

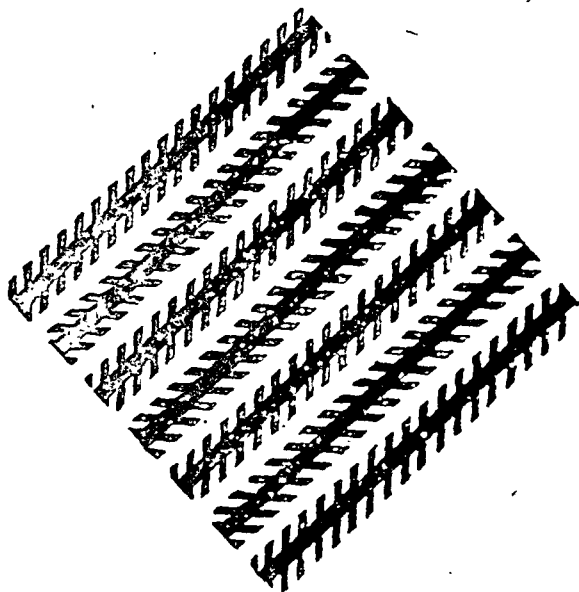


FIG. 279.—Zöllner's lines.

in the retina. Moreover, as previously pointed out, each cone in the macula lutea is connected to a separate chain of neurones.

The importance of binocular vision is very great. If an object is looked at with one eye only, it is impossible to estimate its distance by the sense of vision alone. For instance, if one eye is closed and the other looks at a wire or bar, it is impossible to tell whether, if someone drops a small object, it falls in front of or behind the bar.

Visual judgments are not always correct; there is a large number of puzzles and toys which depend on visual illusions. One or two of the best known are represented in the diagrams on p. 773.

In fig. 278, A, B, and C are of the same size; but A looks taller than B, while C appears to cover a less area than either. The subdivision of a space or line increases its apparent size or length. In fig. 278 D, ab is equal to bc . Vertical distances also are usually overestimated. In fig. 279 the long lines are parallel, though they do not appear so, owing to the influence of the intercrossing lines.

GENERAL REFERENCES.—Duke-Elder, Byrne.

CHAPTER LVII

THE DUCTLESS GLANDS

MOST glands have an external duct through which their secretion passes, but the ductless glands, as their name suggests, pour their secretion internally * into the lymph and the blood-stream. Some glands, such as the pancreas, produce both an external and an internal secretion.

In the very difficult study of the functions of the glands a number of courses have been adopted, and each has been applied with varying success to each of the glands. (1) Removal of the gland; this may be done surgically, or a functional removal of the gland may occur as a result of disease. (2) The administration of the gland or its extracts to man and animals or the study of pathological or artificially induced increases in the activity of the gland. (3) The study of its histology and development in the animal, and in different animals, also has been of value in throwing light on its functions.

Some of the substances elaborated by the gland are very active but others act very slowly; practically all are present in too small amounts even in the blood leaving the gland to permit of reliable chemical assay.

Biological methods of assay have to be used. The substances elaborated by the glands are known as hormones.

Some of the ductless glands have already been studied in relation to their chief functions, *e.g.* the thyroid in relation to general metabolism, and the pancreas in relation to carbohydrate metabolism. The pituitary body and adrenal glands have more generalised activities.

General books on the subject have been written by Sharpey-Schafer and by Vincent, who give the historical aspects.

OTHER GENERAL REFERENCES.—Harrow and Sherwin, Zondek, Hogben, Engleback.

THE ADRENAL GLANDS.

These are two triangular bodies, each resting upon the upper border of the kidney.

* Hence the term "endocrine" given by Sharpey-Schafer.

The gland is surrounded by an outer sheath of connective tissue and consists of an outside firmer cortex and an inside soft, dark medulla. Each portion is developed separately.

(1) The **cortex** is divided into columnar groups of cells (*zona fasciculata*). Immediately under the capsule, however, the groups are more rounded (*zona glomerulosa*), while next to the medulla they have a reticular arrangement (*zona reticularis*). The cells are polyhedral, each with a nucleus, and contain lipoid globules.

(2) The **medulla** consists of a coarse meshwork of fibrous tissue, in the alveoli of which are masses of multinucleated protoplasm, numerous blood-vessels, sinusoids, and an abundance of nerve-fibres and cells.

The tissue of the adrenal medulla is often called *chromaphil* tissue, on account of the ready way in which it stains with chromic salts. Such tissue is, moreover, not confined to the suprarenal, but is found in scattered patches in the retro-peritoneal region and in many sympathetic ganglia, especially in the abdomen. The histological resemblance is accentuated by the presence of numerous sympathetic cells in the suprarenal medulla. The chromaphil tissue wherever found always yields adrenaline.

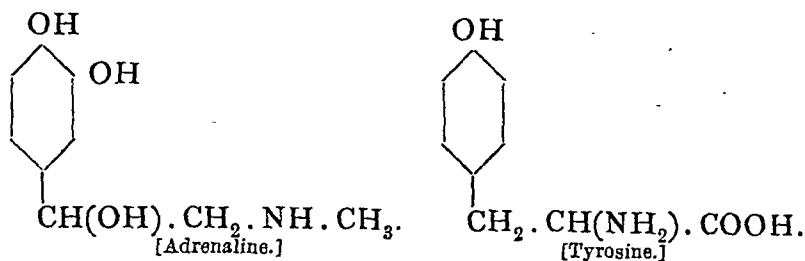
The importance of the adrenal bodies was first indicated by Addison, who, in 1855, pointed out that the disease now known by his name is associated with pathological alterations of these glands. Brown-Séquard found a few years later, that removal of the suprarenals in animals is invariably and rapidly fatal. The symptoms are practically the same (although more acute) as those of **Addison's disease**, namely, great muscular weakness, loss of vascular tone, and nervous prostration. The pigmentation (bronzing) of the skin, however, which is a marked symptom in Addison's disease, is not seen in animals. These experiments have been confirmed, but more and more evidence has accumulated to show that it is the cortex rather than the medulla which is essential to life.

The Functions of Adrenal Medulla.

The vasoconstrictor action of extract of adrenal medulla was discovered in 1893 by Oliver, a practising physician in London who found that it constricted the radial artery of his child! Its action was subsequently studied by him and Schafer, then Professor of Physiology at University College, London, and subsequently at Edinburgh, and since that time a large amount of work has been done.

Adrenaline.—The active principle may be extracted from the medulla of the gland and has been isolated by Takamine and

synthesised. It is shown to be closely related to tyrosine, but the exact significance of this fact is not yet understood.



Its various actions suggest a preparation for muscular activity.

The Action of Adrenaline.

Effect on the Circulation.—If a large dose (0.5 c.c. of 1-1000 solution) is injected intravenously it causes a marked rise of blood-pressure, as a result of great constriction of the arterioles and, probably, of the capillaries (fig. 280). If the vagus nerves have been cut the effect on blood-pressure is still greater, since the drug then causes the heart to contract with greater force and speed. This effect may be best shown on the isolated heart perfused with Locke's solution. The slowing of the heart when the vagi are intact is due partly to the operation of the depressor and carotid reflexes (Heymans), and partly to direct action of the drug or increased cranial pressure (Anrep and Starling) on the vagus centre.

Small doses (1-1,000,000 to 1-100,000), however, which probably imitate more faithfully the normal physiological secretion, may have little or no effect on the blood-pressure but, as indicated in fig. 280, they very materially influence the distribution of blood in the body, transferring it into the muscles from the skin. Such small doses of adrenaline in etherised animals cause a fall of blood-pressure, due it appears to the skin and alimentary vessels being thrown out of action by the ether and to the fact that the effect on the vessels of the muscles is able to show itself (Dunlop).

The vasoconstrictor action of adrenaline appears to be most particularly marked on the vessels of the alimentary canal and the skin, although, in large doses, it probably constricts all vessels. If a limb is skinned, moderate doses, as shown by the plethysmograph, cause the vessels to *dilate*, although the control normal limb diminishes in volume. The coronary vessels like those of the muscles are dilated (fig. 280).

The effect of a large dose on the intestinal vessels is difficult to interpret. If applied directly to them, or perfused through them, it constricts, but in the intact animal there is usually a dilatation of,

a piece of intestine placed in a plethysmograph. The exact cause of this is a subject of debate.

If a large dose of adrenaline is injected subcutaneously into

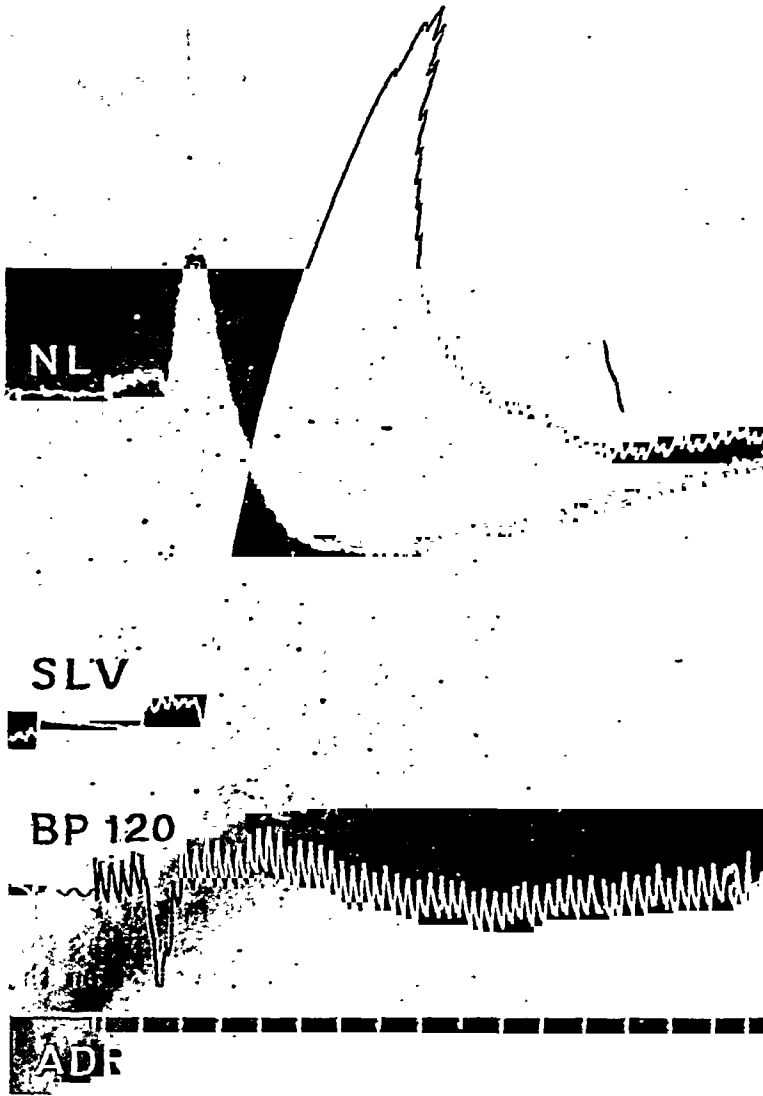


FIG. 280.—Record of volume changes of a skinned limb, SLV, and of an intact limb, NL, and of the blood-pressure of an animal to which a minute dose of adrenaline has been administered intravenously. The skin constriction and muscle dilatation are well seen and cannot be ascribed to changes in blood-pressure, since these are negligible. (McDowall.)

unanæsthetised animals, the rise of blood-pressure may persist for several hours as the absorption is slow.

The motor actions of adrenaline but not the inhibitory are reversed by ergotoxine and ergotamine.

Effect on Metabolism and Respiration.—Adrenaline has also an important action in the mobilisation of glucose. It reduces the glycogen in the liver, at the same time causing a hyperglycæmia and consequent glycosuria. It thus counteracts the effects of insulin.

It has been shown also to increase the metabolic rate. In the unanæsthetised animal, or in an animal which has been allowed to rest under chloralose anæsthesia, a marked and prolonged increase of respiration is evident; but whether this is secondary to the metabolic effect is not clear.

This is to be distinguished from the better known "apnoea," which occurs immediately after the injection of a large dose of adrenaline, and which has now been shown to be due to impulses which pass up in the vagus and from the carotid sinus as a result of the rise of blood-pressure (Heymans, Samson Wright).

Effects on the Alimentary Canal.—If a piece of intestine is placed in a bath of Ringer's solution (which contains in addition phosphate ions), spontaneous contraction occurs. This is stopped by very minute (1-1,000,000) doses of adrenaline. This and other experiments indicate that the movements of the alimentary canal are brought to a standstill by the action of adrenaline. The sphincters, ileocolic and pyloric, are stimulated and food is thereby prevented from moving from one region to another (Elliott). The muscularis mucosa is also stimulated (Gunn).

Other Effects.—Adrenaline also causes dilatation of the bronchi, and for this reason it is extensively used in the treatment of spasmodic asthma. Applied locally it also abolishes anaphylactic reactions to foreign proteins (see p. 794).

Although it has been established that adrenaline has no effect on muscle tone, it does have an effect in improving muscular contraction (Schafer), and in diminishing muscle fatigue (Nice and Cannon). In part this may be due to improved circulation, but adrenaline has been shown to have a beneficial effect on metabolism.

Adrenaline dilates the pupil and erects the hairs in lower animals. The dilatation of the pupil occurs after all nerves to the eye have been cut; indeed, if the nerves have been allowed to degenerate, the pupil reaction becomes more sensitive than before, a fact which shows clearly that adrenaline, although it acts like the sympathetic, does not act on nerve-endings but possibly through an intermediate substance. It does not, however, dilate the pupil like atropine if applied directly to the eye. No doubt vasoconstriction interferes with its absorption.

In amphibia, adrenaline causes a contraction of the pigment cells of the skin, causing the animal to be pale in colour. The one sympathomimetic action which adrenaline lacks is on the sweat glands.

The Destruction of Adrenaline.—Adrenaline is destroyed in the liver very rapidly. In solution, especially if dilute and alkaline, it rapidly becomes oxidised and loses its potency.

Development of the Adrenal Glands.—The relationship to the sympathetic is also seen in the mode of development of the gland. The *medulla* of the organ is developed, quite separately from the cortex, from that part of the neural crest which subsequently becomes differentiated into the sympathetic and the posterior root ganglia. It is, therefore, of interest that sensory stimulation, adrenaline, and stimulation of the sympathetic all bring about similar reactions.

The medulla gradually grows into the *cortex* which is developed in relation to the upper part of the Wolffian body and therefore to the ovary and testis. In certain fishes this amalgamation does not take place, and so in them it has been possible to note the effects of removal of one part or the other. From these experiments, and from others in mammals where operations for removing one part only have been attempted, as well as from the study of disease, the conclusion has been reached that of the two the cortex is the more essential for life.

The Secretion of Adrenaline and Functions of the Adrenal Medulla.—The exact function of adrenaline and whether or not it is circulated in the blood in the resting animal has been much debated. The evidence now appears to be in favour of its being constantly present in the blood in small quantities. At the same time, it is apparent that it is not essential for the maintenance of blood-pressure since animals can be kept alive if the adrenals are removed and the hormone of the cortex administered.

A large number of facts, however, go to show that it may be thrown into the circulation in greater amounts under conditions of stress.

The secretion of adrenaline may be studied in a variety of ways:—

1. The denervated pupil.
2. The denervated heart. These two methods were those used by Cannon, Professor of Physiology in Harvard, U.S.A., and his associates, to whom we owe so much on this subject. The organs are denervated and the effect of certain procedures is studied before and after removal of the adrenals. We know, however, as pointed out by Cannon, that these results do not exclude the secretion of sympathin at sympathetic nerve-endings. The pupil is dilated and the heart accelerated when adrenaline is secreted.

3. The isolated intestine may be studied after the manner described on p. 468. Its movements are inhibited by solutions containing a concentration of 1-1,000,000 adrenaline. The method applied to blood from the adrenal vein was extensively used by Stewart and Rogoff of Western Reserve University, U.S.A.

4. The most unequivocal results were obtained by Tournade (1925), Professor of Physiology in Algiers, who circulated the adrenals of an animal (A) with blood to and from another animal (B) upon which the effects on the pupil, heart, and blood-pressure of certain procedures applied to A were noted.

By these various methods it has been shown that the adrenals are under the control of the splanchnic nerves which cause secretion. Asphyxia and anything which stimulates the sympathetic acts similarly, *e.g.* severe exercise or a fall of pressure in the carotid sinus. The effects of fear and anger in a cat approached by a dog produce acceleration of the denervated heart, dilatation of the denervated pupil, a rise of the blood sugar (see p. 482) and increased respiration. Cannon, therefore, has maintained that adrenaline is secreted under conditions of emergency and emotional stress. Stewart and Rogoff, on the other hand, claimed that adrenaline is secreted in small quantities during rest, and in fact their strenuous opposition to Cannon led to the latter's discovery of sympathin. Tournade, however, has shown that under the usual experimental conditions both views are probably right, for he found that the normal resting secretion could be inhibited by stimulation of the carotid sinus or of the central end of the aortic depressor nerve.

It will be seen that the secretion of adrenaline will be of considerable advantage in augmenting the action of the nervous mechanisms and, in exercise, that of carbon dioxide, in increasing the heart rate, metabolic rate, blood-sugar, and respiration.

Its activity is potentiated by previous treatment of an organ with acetyl-choline.

Adrenaline is probably of considerable value in the protection of the body against cold and in fever (Cramer, Britton and others). If the adrenals are removed a given amount of cold causes much greater shivering than normally, and the amount of adrenaline in the glands is found to be much less than the normal resting value. No doubt the action of adrenaline assists in protecting the animal against cold by constricting the vessels of the skin.

Another important function of the suprarenal is undoubtedly the annulling of the effects of toxic substances, such as histamine, which may be absorbed from the intestine or from wounds. Histamine is the degradation product of the amino-acid histidine, which is produced by the digestion of protein. It may also be demonstrated that under suitable conditions there may be a secretion of adrenaline when histamine is injected intravenously (Dale and Burn). In certain circumstances the rise due to adrenaline secretion may be very prolonged.

Sympathin.—When blood-vessels are constricted by vasomotor nerves there is evidence that a clinical substance is released which

acts as a humoral transmitter and causes constriction of denervated vessels. Some investigators consider that this substance is adrenaline, *e.g.* Bacq of Liege, but others, notably Cannon and Rosenbleuth, find that it is different and prefer the name *sympathin*. The fact that section of the abdominal sympathetic dilates the vessels of the muscles of the hind leg suggests that unlike adrenaline it does not dilate the vessels of muscles.

REFERENCES.—Sharpey-Schafer, Cannon, Grollman, Britton.

The Adrenal Cortex.

The precise function of the suprarenal cortex is still unknown but it is evident that most of the disturbances brought about by disease or removal of the adrenals are due to loss of the function of the cortex, for it has now been found possible to keep adrenalectomised animals alive by administering extracts of the cortex. Such extracts have been prepared by Swingle, Pfiffner, Hartman and others, but more recently Verzár has found that similar results can be brought about by the giving of vitamin B. or flavinphosphoric acid.

In most experiments the rat has been used, as this animal lives for about a week after the organ is removed.

(1) The cortex is particularly rich also in vitamin C, having three times the amount of ascorbic acid present in orange juice (Szent-Györgyi). The presence of such a strongly reducing substance suggests that it may be concerned in preventing the destruction of the very easily oxidised adrenaline of the medulla.

(2) There is reason to believe that the hormone is intimately concerned with the water-salt balance in the body. After adrenalectomy sodium and water are lost from the body and dehydration occurs. The administration of sodium chloride to patients with Addison's disease is very beneficial. How the hormone acts is unknown; it may be by affecting membrane permeability. In death from adrenalectomy blood concentration is a marked feature. As a result of the loss of sodium there is a marked diminution of the alkali reserve which probably reduces neutral fat absorption by lessening the alkali available for soap formation.

(3) The hormone is concerned also in the protection of the animal against the effects of histamine absorption, for removal of the cortex renders a cat specially sensitive to its toxic effects (Dale, Kellaway and Cowell). It has been claimed that death after adrenalectomy is due to the capillaries becoming excessively permeable. The lipides of the membranes may be involved.

(4) The cortex has some important relation to the reproductive system, as is suggested by its development. Evidence of this is

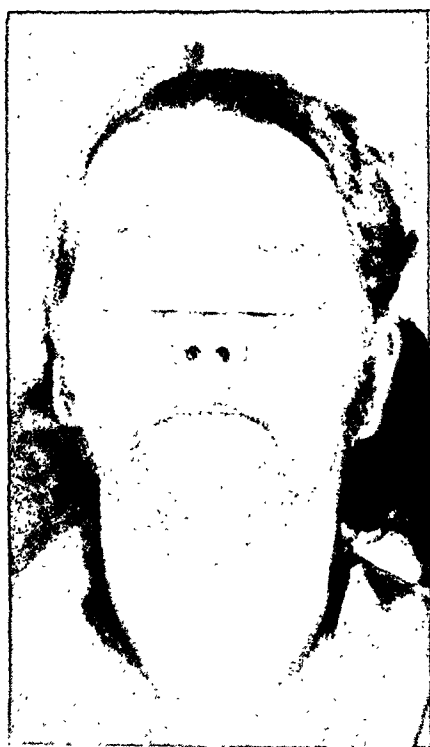
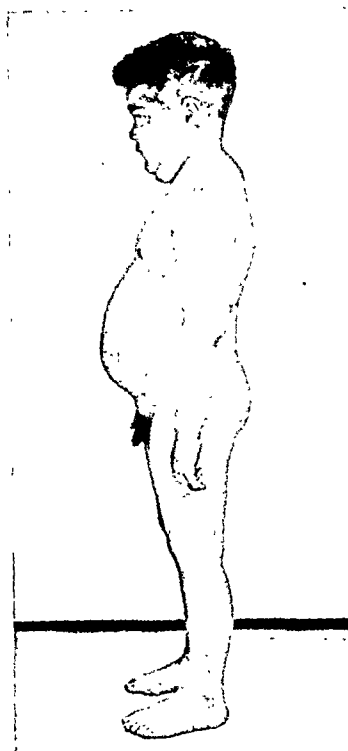


FIG. 280a.—Cases of tumour of the adrenal cortex. Above, a boy of 9 showing sexual precocity. Below, a woman suffering from virilism before and after removal of the tumour. (Broster.)



FIG. 280B.—Case of acromegaly, showing successive stages. (Sharpey Schafer.)

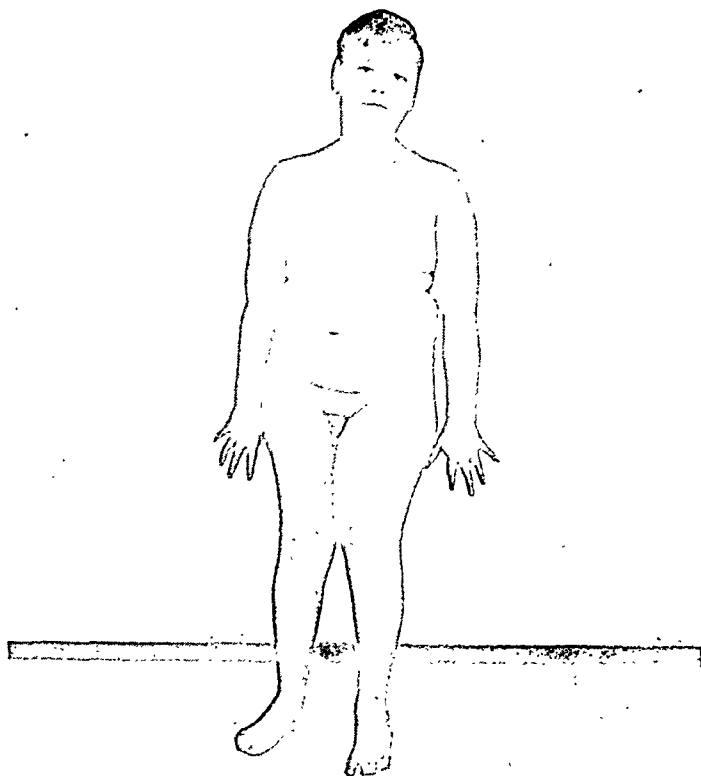


FIG. 280C.—Case of hypopituitarism. (Fröhlich type.) (S. L. Simpson.)

seen in the fact that tumour-overgrowths of the cortex lead in male children to premature development of the sexual organs and pubic hair, and in females to the appearance of masculine characters, such as the growth of hair, enlarged clitoris and diminution of the breasts (fig. 280A). When this occurs in adults (virilism) histological changes in the cortex are found at death (Vines). It seems possible that this is related to the high lipide and choline contents of the cortical cells. The cortex is appreciably larger in the female than in the male and enlarges in pregnancy when the blood cholesterol is increased. This suggests that it has some importance in regulation of body activities during pregnancy.

M'Carrison emphasises also that the cortex is antagonistic to the thyroid.

In conclusion, it may be suggested that probably the functions of the cortex are not so diverse as at present appear. It may be that eventually these various activities of the hormone will be shown to be due to the cortex having some fundamental action affecting many processes similarly.

The Active Principle of the Cortex.—The most important principle so far isolated from the cortex is known as corticosterone, which is a sterol closely related chemically to the progesterone of the corpus luteum (p. 811), with which it is to some extent mutually replaceable, each having the effect of the other. It prolongs the life of adrenalectomised animals. The presence of other hormones having various actions like those of the pituitary below have also been described.

REFERENCES.—Broster and Vines, 1933; Swingle, 1932.

THE PITUITARY BODY.

This occupies the sella turcica of the sphenoid bone. It may be divided into several parts, which show developmental, structural, and functional differences. Its first description was given by P. T. Herring (1908) of St Andrews, and this has subsequently been elaborated by Ranson (1937), Professor of Neurology in North-Western University, U.S.A. See fig. 281, p. 784.

(1) *The anterior lobe* is developed as a tubular prolongation from the ectoderm of the buccal cavity, but the growth of intervening tissue soon cuts off all connection with the mouth. It consists of columns of cells separated by blood sinus. The cells are of three types, acidophil (staining with acid dyes), basophil staining with basic dyes, and chromophobe, which have little affinity for dyes. An overgrowth of each type may occur and produce specific symptoms.

(2) *The posterior lobe.*—This is connected to the floor of the third ventricle, of which it forms a developmental outgrowth; in some animals (cat) it remains hollow throughout life, in others (dog) the neck alone remains hollow, and in most (including man) both body and neck are solid, with traces of a cavity in the neck. Though developed from the brain, it contains in the adult no nerve cells, but consists mainly of neuroglia. It is surrounded and invaded by the epithelial cells and colloid matter derived from the *pars intermedia*. It plays the part of a gland in virtue of these epithelial cells.

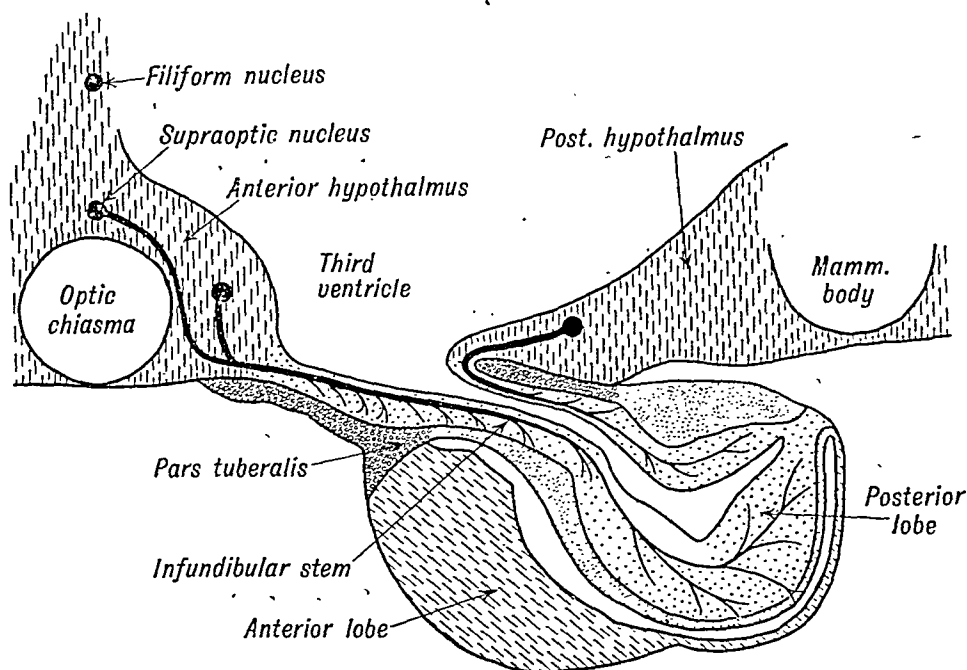


FIG. 281.—Diagram of the Pituitary Body. (After Herring and Ranson.)

(3) *The pars intermedia.*—This lies between the anterior and posterior lobes, and forms a closely fitting investment of the latter lobe. It is developed in association with the anterior lobe, and consists of finely granular cells arranged in layers closely applied to the body and neck of the posterior lobe and the undersurface of adjacent parts of the brain. Colloid material occurs between the cells and passes into the interior of the posterior lobe, and so into the cerebrospinal fluid third ventricle of the brain.

(4) *The pars tuberalis.*—This surrounds the stalk by which the pituitary body is connected to the brain, at the tuber cinereum just in front of the optic chiasma. It has a glandular structure and is very vascular and has a special importance because tumours of this region lead to a great deposition of fat and upset of carbohydrate

during the growth of the long bones, and is characterised by excessive stature of the individual who is otherwise normal. The Irish giant, described by John Hunter in the eighteenth century, and now in the Hunterian Museum, has a markedly enlarged sella turcica.

Acromegaly.—Acidophil hyperactivity developing after the union of epiphyses gives rise to this condition. The long bones are unable to lengthen, but enlargement of the skeleton as a whole occurs, being most marked in the lower face, hands, and feet; the nose is enlarged, the malar bones become more prominent and the jaws become massive, separating the teeth. The hands and feet may become enormous. Thickening of the soft parts occurs also, and accentuates the grossness of the face (see fig. 280B) and extremities. The American “ugliest woman in the world” was a typical acromegalic. A gorilla-like appearance results from the protruding jaws, the bent spine and the large hands hanging down to the knees. The increased basal metabolism is considered to be due to thyrotropic action. It will be readily understood that gigantism and acromegaly frequently occur together.

Cushing's Syndrome.—The symptoms vary much. Prominent are adiposity (excluding the limbs), genital dystrophy, polyuria, glycosuria, and extreme thirst. Cushing correlates it with basophil adenoma of the anterior lobe.

Underactivity—*Lorain-Levy Infantilism* is considered to be due to anterior lobe deficiency, more especially of the growth-producing and gonadotropic hormones. The not unattractive midgets seen at shows with perfectly formed miniature bodies and infantile sex characteristics are of this type.

Simmonds' disease is due to a destructive lesion of the anterior lobe, and the symptoms probably represent a general endocrine failure from the lack of the stimulating pituitary hormones; thus we get general bodily wasting, including the viscera, premature old age, loss of sexual power or sterility, low blood-pressure, and intense debility. The condition known as progeria, characterised by precocious senility, is probably due to identical causes occurring before puberty. The child looks like a wizened old man, but more commonly the state occurs in women from forty to fifty and is very like Addison's disease. It has been successfully treated by the administration of the adrenotropic of the pituitary.

The loss of weight is produced in rats whose pituitaries have been removed, probably because of excessive carbohydrate metabolism, and may be similarly cured. (Hemphill and Reiss, 1944.)

The following three conditions are due to lesions not so definitely located as the foregoing, but involving the pituitary and hypothalamic regions.

Brissaud Type.—This was originally described by Brissaud as due to hypothyroidism, but it is now considered that the pituitary and possibly the hypothalamus is primarily at fault. The fat boy of the *Pickwick Papers* probably represents a typical case. The signs are not unlike those of tumours of the adrenal cortex and of the parathyroid which may also be involved. There is a progressive increase of the fat of the upper part of the body, undeveloped sexual organs, absence of hair except on the head and a strong somnolent tendency.

Dystrophia Adiposo-genitalis (Fröhlich's Syndrome).—Many lesions involving the pituitary and neighbouring structures have been held accountable for this condition. The signs and symptoms naturally vary but great increase of fat and non-development of sexual organs are constant. In males, female characteristics predominate and the testes may not descend. There is an increased tolerance to carbohydrates. (See fig. 280c.)

Diabetes Insipidus.—As indicated above, polyuria, great thirst, and wasting characterise this disease. A large number of lesions involving the base of the brain have been described as causative factors; in many the hypothalamus has been involved. The controlling influence of pituitrin on the polyuria would indicate a posterior lobe deficiency, but from what has been said above it may be inferred that a hypothalamic lesion may produce a like result.

The study of the functions of this gland are much complicated by anatomical considerations.

1. Owing to the intimate connection of the several portions of the gland to one another a clear-cut picture of the result of a lesion in any one portion is rarely produced either experimentally or clinically.

2. A glance at a median section of the base of the brain will show the relation of the pituitary gland to the optic chiasma and the hypothalamus. A pituitary tumour involving the former will produce hemianopsia, usually bitemporal (see fig. 276). Involvement of the hypothalamus, including the tuber cinereum, will produce symptoms peculiar to these structures, *e.g.* somnolence, obesity, polyuria, genital hypoplasia, which symptoms are familiar in pituitary disturbance. Even though the hypothalamus is not directly involved by the pituitary lesion it may be indirectly affected by alteration in the hormones; thus anterior lobe hormones are carried to the hypothalamus by the hypophysis-portal system of vessels which break up into capillaries again in the latter region, the secretion from the pars intermedia may traverse the hypothalamus en route *via* tissue spaces of pars nervosa infundibulum to the 3rd ventricle. To the hypothalamus, as mentioned previously, is ascribed an intimate association with pituitary activity. According

to our present knowledge, therefore, "hypothalamo-pituitary" interconnection is three-fold:—

- (i) A pituitary tumour may involve the hypothalamus.
- (ii) A hypothalamic lesion may block the transit of pituitary secretion into the system generally.
- (iii) By sympathetic (or parasympathetic) involvement a hypothalamic lesion may give rise to symptoms ascribed to pituitary dysfunction.

3. The discovery of gonadotropic, thyrotropic, and adrenotropic hormones in the anterior lobe, and also of Simmonds' disease (q.v.), has an important bearing on the subject of multi-glandular syndromes.

The Hormones of the Anterior Lobe.—It is now usual to consider that the anterior lobe contains a group of hormones. How far they are really all different is as yet difficult to say, but they are convenient pegs on which to hang existing knowledge. They are given in their probable order of importance.

1. The *growth* hormone has already been discussed. Its source appears to be the acidophil cells.
2. The *gonadotropic* hormone (Prolan) shows its various effects on ovulation and is discussed in relation to the ovary and testis. The basophil cells may produce it, but this is not certain.
3. The *lactogenic* hormone promotes the secretion of milk in mammary glands already prepared by the oestrogens and progesterone of the ovaries.
4. The *thyrotropic* hormone is indicated by the following facts. Removal of the thyroid leads to increased pituitary growth. A hormone can be extracted from the pituitary which produces the effects of hyperthyroidism. It has no effect on thyroidectomised animals, therefore must be considered to stimulate the thyroid gland.
5. The loss of the *adrenotropic* hormone is seen in the atrophy of the adrenal cortex when the pituitary is removed or diseased, while the injection of anterior lobe causes hypertrophy. (See Swann.)
6. The *metabolic* hormones are concerned chiefly with carbohydrate metabolism. Possibly the most striking evidence of the relationship is seen in the absence of diabetes in an animal in which both the pituitary and pancreas have been removed. We have already remarked on the increased carbohydrate tolerance in Fröhlich's syndrome

and the great sensitivity to insulin of animals in which the pituitary is removed. It has also been found that the administration of the extracts leads to pancreatic degeneration and diabetes (Young), but since several other substances, *e.g.* alloxan, or extract of parotid, produce similar results it is not certain that the pituitary action is of special significance. It may well be that there are distinct hormones—increasing resistance to insulin and acting directly on the pancreas—but admittedly the evidence is all too new to be correctly assessed.

The Posterior Lobe and Pars Intermedia.—These do not appear to be so important for life, but they elaborate the substance **pituitrin**, which causes some very characteristic reactions. Much of the early work was carried out with watery extracts, which contain also the depressor substances present in most tissues; but by preliminary alcoholic extraction these can be removed, and a purer substance is thus obtained. The active principle of the posterior lobe is destroyed slowly by boiling but it deteriorates in solution.

Effect on the Circulation.—The effect of intravenous injection in animals is to produce a marked temporary rise of blood-pressure, which, however, is much more prolonged than that due to adrenaline and not reversed by ergotoxine. There is marked contraction of all the arterioles in the body with the possible exception of those of the kidney. The constriction of the skin vessels is very marked, and often the pallor caused thereby creates alarm, although it has not necessarily any serious significance. Local pallor occurs if the substance is injected intradermally. In spite of this vasoconstriction the blood-pressure of man does not rise appreciably, if at all, indicating that there is considerable vascular compensation. The slowing of the heart, which takes place, may be part of the compensation. Similar compensations are presumably responsible for the return of the blood-pressure to normal in animals, since further injections do not cause the same rise of pressure for some time. At the same time, it must be emphasised, that it is not known whether this vascular action of pituitary extract is in any way related to the normal function of the gland.

Effect on the Kidney.—In man, or unanaesthetised animals, the injection of the extract causes a reduction in the amount of urine and, for this reason, pituitrin may be used to reduce the amount of urine in *diabetes insipidus*, a condition in which large quantities of dilute urine are passed and which is sometimes associated with lesions in the region of the pituitary body. The condition of diabetes insipidus has now been produced experimentally by the removal of the posterior lobe, and this fact, and the effects of extracts, suggest that this part of the pituitary secretes an anti-

diuretic hormone; but since the diuresis does not occur if the whole pituitary is removed it would seem that a diuretic hormone is produced by the anterior lobe. In normal man the antidiuretic effect may be conveniently observed by studying the diuresis produced by the ingestion of a quantity of fluid (a) normally and (b) accompanied by an injection of the extract.

In anæsthetised animals, pituitary extract increases the flow of urine, apparently as a result of dilatation of the kidney vessels. This fact is not related to the rise of blood-pressure which may be caused; since it may be brought about by later doses, which do not cause the rise.

Effect on the Uterus (oxytocic action).—Of all varieties of plain muscle uterine appears to be the most sensitive and therefore the uterus of the virgin guinea-pig is used for purposes of the **standardisation** of extracts of unknown strength. It is suspended in oxygenated Van Dyke's solution after the manner described for the intestine (p. 468). The extract is standardised by comparing the contraction produced by an unknown sample with that caused by a standard sample; extraordinary dilute solutions (1-10,000,000) of pure extract cause contraction. "Oxytocic" means "quickenning delivery," and the extract is used with due precautions in obstetrics; but too large doses have been known to cause rupture of the uterus. The fact that cerebrospinal fluid gives the oxytocic test suggests that the pituitary secretion enters that fluid. It has been suggested that such pituitary secretion is responsible for the onset of labour, but since its injection does not cause labour in an animal not at full time it is evident that other factors are concerned. One of these is the presence of œstrin, the œstrus producing hormone of the ovary. If œstrin is applied to the isolated uterus the action of pituitary extract is enhanced. A product "pitocin" is claimed to be almost free from the vasoconstrictor ("pitressin") fraction.

Effect on other Plain Muscle.—Now that pituitary extract is made quite free from histamine it has become evident that it is not a generalised plain muscle stimulant as was previously thought. It does, however, stimulate the intestine and causes milk to be driven out of the lactating mammary gland. This is brought about by the vasopressor factor.

Effect on Pigment Cells of Amphibia.—Unlike adrenaline, pituitary extract injected into a frog causes a darkening of the skin from dilatation of the melanophores. This result is brought about with very small doses—a fraction of a cubic centimetre of a one in a million solution—and it may therefore be used as a test. Removal of the posterior lobe in the frog, on the other hand, causes constriction of the skin melanophores and, consequently, pallor. The

substance which produces this effect appears to be concentrated in the pars intermedia. (Hogben and Winton).

Effect on Carbohydrate Metabolism.—As we have seen in relation to the anterior lobe, undergrowth of the pituitary body is associated with the accumulation of fats and a high sugar tolerance. What exact part the pituitary plays in carbohydrate metabolism is not clear, but certain experimental facts are outstanding. Posterior extract may cause a slight rise of the blood-sugar, and has the power of antagonising insulin (Burn). It has also been shown by Houssay of Buenos Aires that if the pituitary is removed at the same time as the pancreas, diabetes mellitus is no longer caused, and the animal is abnormally sensitive to insulin.

Houssay appears, however, to relate this to the anterior lobe which increases the formation of glucose from fat or protein. Extracts cause a decrease in the blood fat and in liver fat.

The Control of the Pituitary Body.—As yet there is little known of the subject, but there is increasing evidence, especially by a group of Chinese workers, Chang Huang and Wang (independently), that it may be reflex, for stimulation of the central end of the vagus causes the appearance in the blood of the pituitary hormones. It has been shown that coitus in the rabbit causes ovulation through the activity of the pituitary. It may be that its activity is increased by sexual emotions generally.

Looking at the subject generally and considering the general anatomical relationship of the pituitary, together with the action of its various hormones, it is difficult to escape from the conclusion that the pituitary is primarily concerned with growth, reproduction, and also the adjustments necessary for the nourishment of the foetus. In this connection it may be noted that in the eel considerable seasonal variation is seen. The organ increases in size at puberty and in pregnancy. If the animal is not allowed to migrate the pituitary becomes much enlarged.

THE THYMUS.

This gland attains its greatest size soon after birth, and after the second year it gradually diminishes, until in adult life hardly a vestige remains; it is then replaced by adipose and connective tissue.

The gland is composed of lymphoid tissue surrounded by a fibrous capsule from which processes carrying blood-vessels and lymph-vessels pass in to divide it up into lobes, lobules, and follicles. Scattered in the lymphoid tissue of the medulla are the *concentric corpuscles of Hassall*, which are nests or islands of epithelial cells cut off from the epithelium of the pharynx in process of development.

In hibernating animals, in which it persists throughout life,

the gland enlarges, and its cells become laden with fat as each hibernating period approaches.

Castration retards the atrophy of the thymus, whilst removal of the gland hastens the growth of the testes, a fact which suggests some relationship with the generative organs.

The thymus is not essential to adult life; indeed, the evidence is now very complete that its persistence into adult life may be associated with dire consequences. Persons in whom it persists are specially liable to die under anæsthesia (*status lymphaticus*), and to suffer from *myasthenia gravis*, a condition of progressive loss of power of muscular contraction due either to a failure to elaborate acetyl-choline in adequate amounts or to an excessively rapid destruction of this substance. The condition is relieved by substances like eserine and prostigmine which prevent the destruction of acetyl-choline.

The Pineal Gland.

This gland, which is a small reddish body, is placed beneath the corpus callosum, and rests upon the corpora quadrigemina. It is composed of tubes and saccules lined and sometimes filled with epithelial cells, and containing deposits of earthy salts (brain sand). A few small atrophied nerve-cells without axons are also seen.

In certain lizards, such as *Hatteria*, and in certain fishes such as the lamprey, the pineal outgrowth is better developed and may be paired. One division corresponds to the pineal gland; the other becomes developed into an eye-like structure connected by nerve-fibres to the habenular ganglion; this third eye is situated centrally on the upper surface of the head but is covered by skin.

The chief claim the pineal gland has to be considered an endocrine organ is that it has possibly some obscure relationship to the development of the sexual organs.

The Carotid Body and Aortic Body.

These are situated, the one at the point of bifurcation of the common carotid artery and the other on the arch of the aorta. They are made up of a plexus of small arteries, and are enclosed and supported by fibrous tissue. They contain also polyhedral cells collected into spheroidal clumps. Some of the cells of the carotid gland stain brown with chromic acid like those of the suprarenal medulla. It has now been found that the aortic and carotid bodies are sensitive to the gaseous content of the blood and act as sensitisers of the respiratory centre (see Respiration) and that extracts contain a vasoconstrictor substance.

General.—From what has been said it is evident that the endocrine organs form important chemical substances for the control of the body, but it must be understood that they themselves are controlled by the nervous system. The advantage of chemical over nervous control of organs is that it can be more generalised and more prolonged. As yet, however, we know very little of the way in which the secretions of the ductless glands are brought into relationship with the requirements of the animal.

HUMORAL SUBSTANCES.

In addition to the hormones elaborated by the ductless glands a number of substances are released in special circumstances. Histamine and choline are the most important but others, *e.g.* P-substances (pain), have been described. In dying tissues many of the amines which appear have a vasoconstrictor action.

Histamine or β -iminazoly-ethylamine is so called because it is so easily produced from the amino-acid histidine when many living tissues are damaged. It may be extracted from the tissues especially from the skin and the lungs. It also occurs in putrefactive tissues but was originally discovered by Barger and Dale in 1910 in their attempt to discover the true nature of the uterus-contracting substance in ergot, the fungus which commonly grows on rye and leads to abortion amongst rye-eating peoples.

The importance of histamine came into prominence when it was pointed out that its injection in quite small doses (5-10 mg. for an average cat) into carnivora led to a state of profound shock from a pooling of the blood in the capillaries which become widely dilated (Dale, Laidlaw, Richards).

It is certainly released in the anaphylactic reaction (see below) and is very akin to the H-substance of Lewis (see Skin Circulation). Certainly a substance with similar action is produced. If injected into the skin it causes a local dilatation of capillaries and a wheal. The great rapidity with which it or a similar substance is released from tissues suggests that it may have an important action in dilating capillaries in active regions such as muscle or in injury to the skin and in anaphylactic reactions.

In addition to dilating capillaries it constricts smooth muscle, notably that of the uterus, bronchioles, and large blood-vessels; in rodents this reaction predominates. It also causes a secretion of gastric juice and has been employed instead of a test-meal, but unfortunately the dilatation of cerebral capillaries produces intense headache. It is of importance, too, because it is very liable to be an impurity in organ extracts, but it may be destroyed by boiling with alkali. That it is antagonised in the animal body by the adrenal gland is suggested by the fact that removal or destruction of the adrenal cortex, like anaesthesia, sensitises the carnivora to its action. It is destroyed by an enzyme histaminase which, according to Best and McHenry, is found especially in the wall of the intestine and the kidney. There is, however, still much to be learned about this interesting substance.

Histamine, being an iminazole derivative, contains the typical ring and gives characteristic reactions. (See Histidine.)

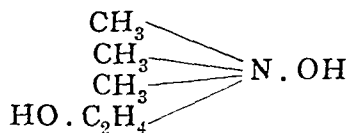
Histamine and the Anaphylactic Reaction.

As first shown by Richet in Paris, if egg white is injected into a dog or guinea-pig it is harmless, but if a second dose is injected three weeks later there is an intense contraction of smooth muscle in the body, especially of the uterus, bronchi (in the guinea-pig) and exit veins of the liver (in the dog), which commonly causes the death of the animal. Similar reactions in man produce some, but not all, asthma and urticaria (nettle-rash). The reaction is probably at the root of many cases of abnormal reaction to articles of diet. The present view is that the foreign protein causes a release of histamine from the tissue sensitised by the sensitising dose occasioned by a temporary fault in digestion (see p. 440).

Choline.—Although choline was one of the earliest natural bases found in animal tissues its importance and that of **acetylcholine** have only been recognised comparatively recently.

The choline or tri-methylamine bases which are derivatives of methylamine alcohols are of physiological interest in that acetylcholine is a normal chemical transmitter released at nerve-endings. They are also parasympathomimetic, *i.e.*, act like the parasympathetic; they slow the heart, dilate arteries, constrict the pupil, and bring about secretion by glands. Their action generally is prevented by atropine. In large doses or after atropine they have the opposite action.

Choline itself may be looked upon as a substituted ammonium hydroxide; one of the hydrogens is replaced by a hydroxyethyl group, and the other three by methyl groups. Its formula is therefore



Choline was first isolated from bile, but its presence in a wide variety of nervous tissues was soon recognised, especially by Halliburton (1898) and his co-workers in King's College, London. Subsequently the activity of the substance led to the extensive study of its compounds by the American pharmacologist Reid Hunt (1909), who found that acetylcholine was as much as a thousand times more active than choline itself as a vasodilator. It brings about vasodilation in a dilution of 1:10,000,000.

The subsequent story of acetylcholine has already been told in relation to the humoral transmission of the nerve impulse.

Acetylcholine may be extracted from a wide variety of tissues and, with histamine, is responsible for the fall of blood-pressure

that so many tissue extracts give. If injected into an animal the duration of its action is very short-lived as it is extremely rapidly hydrolysed through the agency of an enzyme choline esterase, discovered by Steadman (1932) in Edinburgh, which is present in all tissues. Before this reaction was discovered it was not generally realised that biochemical changes could occur so rapidly and its recognition has opened up a new vista, especially in regard to the workings of the nervous system. The story of choline and of histamine are excellent examples of how purely academic work has turned out many years later to be of great importance.

Sympathin.—This substance has already been discussed (p. 781).

CHAPTER LVIII

REPRODUCTION

IN the higher animals reproduction is brought about by the union of male and female cells, known as spermatozoa and ova, which are elaborated by the testes and ovaries of the two sexes, the union taking place in the sexual passages of the female, in which they are deposited by the male during the sexual act known as copulation or coitus which is presumed in animals during a period of mating.

THE MALE REPRODUCTIVE ORGANS.

These consist of the two testes or testicles which produce spermatozoa, and the ducts which lead from them.

The testis is enclosed in a serous membrane called the *tunica*

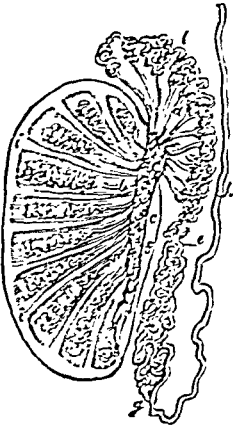


FIG. 282.—Plan of a vertical section of the testicle, showing the arrangement of the ducts. The true length and diameter of the ducts have been disregarded. *a a*, Tubuli seminiferi coiled up in the separate lobes; *b*, tubuli recti; *c*, rete testis; *d*, vasa efferentia ending in the coni vasculosi; *e*, *f*, *g*, convoluted canal of the epididymis; *h*, vas deferens; *i*, body of Highmore; *i i*, fibrous processes running between the lobes.

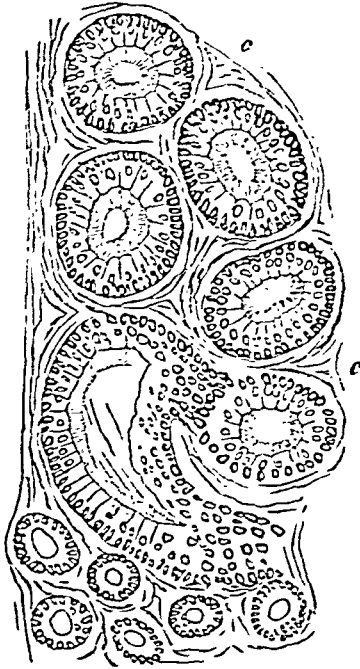


FIG. 283.—Section of the epididymis of a dog.—The tube is cut in several places, both transversely and obliquely; it is seen to be lined by a ciliated epithelium, the nuclei of which are well shown. *c*, Connective tissue. (Schofield.)

vaginalis, originally a part of the peritoneum; which descends into the scrotum before the testis and subsequently gets entirely cut off from the remainder of the peritoneum. There are, however, many animals in which the testes remain permanently in the abdomen.

The external covering of the testicle itself is a strong fibrous capsule, called, on account of its white appearance, the *tunica albuginea*. Passing from its inner surface are a number of septa or trabeculae, which divide the organ imperfectly into lobules. On the posterior aspect of the organ the capsule is greatly thickened, and forms a mass of fibrous tissue called the *corpus Highmoreianum* (body of Highmore) or *mediastinum testis*. Attached to this is a much convoluted tube, which forms a mass called the *epididymis*. This receives the ducts of the testis, and continues into a thick-walled tube, the *vas deferens*, by which the semen passes to the urethra.

Each lobule of the testicle contains several *convoluted* tubes. These tubes commence near the tunica albuginea, and terminate after joining with others in a *straight tubule*, which passes into the body of Highmore, where it ends in a network of tubes, the *rete testis*. From the rete about fifteen efferent ducts (*vasa efferentia*) arise, which become convoluted to form the *coni vasculosi*, and then pass into the tube of the epididymis.

The *convoluted* or seminiferous tubes have the following structure: each consists of (1) an outer wall of flattened connective-tissue cells intermingled with elastic fibres; (2) a fine *membrana propria*; (3) a lining epithelium of several layers of germinal cells. Next to the *membrana propria* is a layer consisting of *spermatogonia* and supporting or nurse cells (*Cells of Sertoli*) which provide nutriment for the developing spermatozoa. More internally, between the projecting processes of the nurse cells, are large *primary spermatocytes*, derived from the division of the spermatogonia. Still nearer the lumen of the tube lie the *secondary spermatocytes*, which are the daughter-cells of the primary spermatocytes; the secondary spermatocytes give rise by division to the *spermatids* which lie next the lumen. The spermatids become embedded in the inner ends of the nurse cells, where they grow and become converted into spermatozoa.

The interstitial connective tissue of the testis is loose, and contains numerous lymphatic clefts. Lying in it, accompanying the blood-vessels, are strands of epithelial cells, of a yellowish colour (*interstitial cells*).

The *straight tubules* consist of basement-membrane and lining cubical epithelium only. The *tubules of the rete testis* are lined by cubical epithelium; but have no basement-membrane. The *vasa efferentia* and *epididymis* are lined by columnar cells, some of which are ciliated, while others are devoid of cilia, and probably possess secretory functions. There is a good deal of muscular tissue in their walls. The *vas* or *ductus deferens* consists of a muscular wall (outer layer longitudinal, middle circular, inner longitudinal), lined by a mucous membrane, the inner surface of which is covered by columnar epithelium.

The *vesiculæ seminales* are outgrowths of the vasa deferentia. Each is a much convoluted, branched, and sacculated tube of structure similar to that of the vas deferens, except that the wall is thinner; their secretion is added to the semen, along with the secretion of the glands of the prostate.

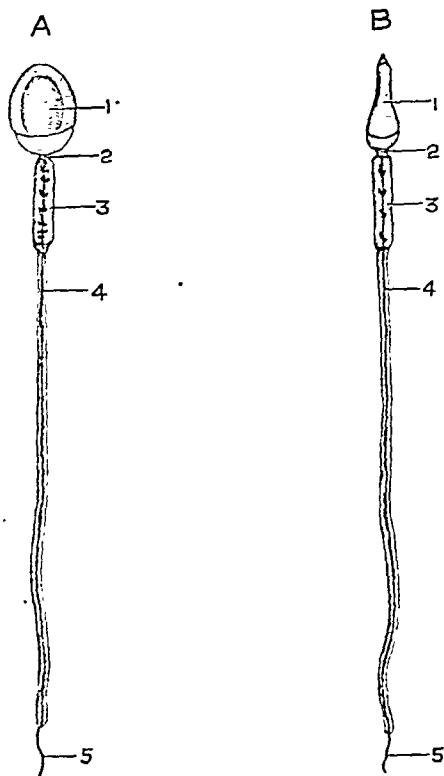


FIG. 284.—Semi-diagrammatic representation of human spermatozoa. A, front view; B, side view. 1, Acrosome, surrounding head; 2, neck; 3, middle-piece; 4, tail; 5, end-piece. The axial filament runs through the body and tail into the end-piece.

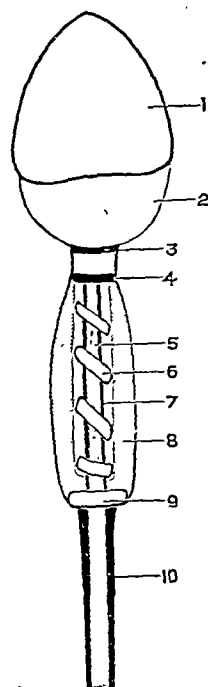


FIG. 285.—Diagram of part of a human spermatozoon highly magnified (after Meves). 1, Acrosome; 2, head; 3, anterior centriole in neck; 4, posterior centriole in neck; 5, axial filament; 6, spiral sheath; 7, sheath of axial filament in middle-piece; 8, mitochondrial sheath; 9, annulus; 10, thick sheath of axial filament in tail.

The *penis* is composed of cavernous tissue covered by skin. The cavernous tissue is collected into three tracts, the two *corpora cavernosa* and the *corpus spongiosum* in the middle line inferiorly. All these are enclosed in a capsule of fibrous and plain muscular tissue; the septa which are continued in from this capsule, form the boundaries of the cavernous venous spaces of the tissue. The arteries run in the septa; the capillaries open into the venous spaces. The arteries are often called *helicine*, as in injected specimens they form twisted loops projecting into the cavernous spaces (see also "Circulation").

The Spermatozoa.—The semen is a richly albuminous fluid in which are suspended the spermatozoa. Each spermatozoon consists of a head, a middle-piece and a tail. The head is oval and flattened. It is composed of a nucleus, in which the chromosomes are so compressed together as to be indistinguishable, and an acrosome. The acrosome forms a cap over the anterior end of the nucleus. The sperm effects entrance into the ovum at fertilisation by means of this acrosome, which probably liberates substances which assist in perforating the zona-pellucida of the egg. The middle-piece is composed of a neck, containing one or two centrioles, and the middle-piece proper. The axial filament of the tail originates in the centrioles contained in the neck immediately behind the nucleus. It traverses the middle-piece and the whole length of the tail. A delicate cytoplasmic sheath surrounds the axial filament throughout the greater part of the length of the tail, but this is absent at the extreme posterior end, which is known as the end-piece.

If kept under suitable conditions spermatozoa will live for thirty days. They are easily killed by dilute acid

THE FEMALE REPRODUCTIVE ORGANS.

These consist of the two ovaries which produce ova, and the uterus with the Fallopian tubes and vagina which are continuous with it.

The Ovary is composed of fibrous tissue (stroma) containing, near its attachment to the broad ligament, a number of plain muscle-fibres. It is covered by a layer of cubical cells, called the germinal epithelium, which, in young animals, is seen dipping down, here and there, into the stroma. The stroma generally contains a number of interstitial cells.

Sections of the ovary show that the stroma is crowded with a number of rounded cells, the *oöcytes*, which are contained in numerous vesicles of different sizes called *Graafian follicles*. The smallest follicles are near the surface, the largest are deeply placed, but as they expand they again approach the surface, and ultimately rupture upon it.

The smallest follicles consist of a single layer of epithelium surrounding the *oöcyte*, and an outer layer of fibrous connective tissue derived from the stroma. In larger follicles the epithelium is many-layered and is known as the **membrana granulosa**. The outer layer is also differentiated into an inner vascular layer, the **theca interna**, and an outer fibrous layer, the **theca externa**. During the later growth of the follicle a cavity, the **antrum**, appears in the membrana granulosa and enlarges until it occupies the major part of the follicle. The cells of the membrana granulosa line this

cavity and form a discus proligerus around the oöcyte which projects into it. The antrum is filled with fluid, the liquor folliculi. The

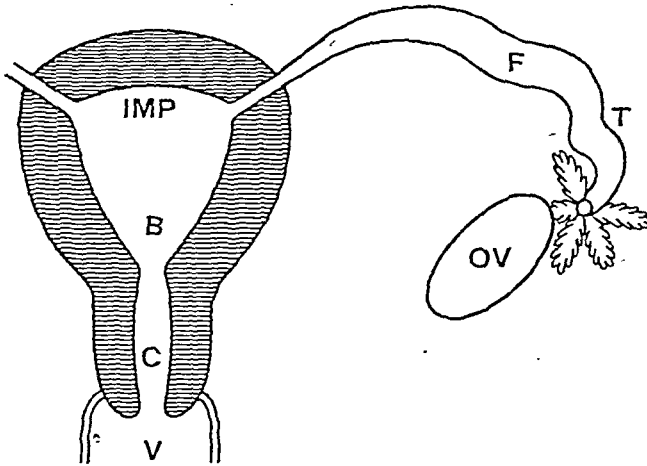


FIG. 286.—Diagrammatic view of the uterus and its appendages, as seen from behind. The uterus and upper part of the vagina have been laid open by removing the posterior wall; the Fallopian tube, round ligament, and ovarian ligament have been cut short, and the broad ligament removed on the left side; *u*, the upper part of the uterus; *c*, the cervix opposite the os internum; the triangular shape of the uterine cavity is shown, and the dilatation of the cervical cavity with the rugæ termed arbor vite; *v*, upper part of the vagina; *od*, Fallopian tube or oviduct; the narrow communication of its cavity with that of the cornu of the uterus on each side is seen; *l*, round ligament; *io*, ligament of the ovary; *o*, ovary; *i*, wide outer part of the right Fallopian tube; *f*, its fimbriated extremity; *po*, parovarium; *h*, one of the hydatids frequently found connected with the broad ligament. $\frac{1}{2}$. (Allen Thomson.)

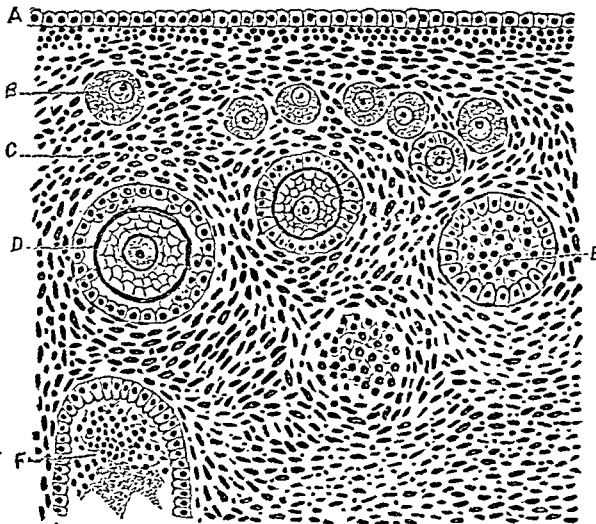


FIG. 287.—Section of the ovary of a cat. A, germinal epithelium; B, immature Graafian follicle; C, stroma of ovary; D, zona pellucida surrounding the primary oöcyte; E, Graafian follicle showing lining cells; F, follicle from which the oöcyte has fallen out. (V. D. Harris.)

Graafian follicle finally ruptures and liberates the discus proligerus with the contained oöcyte, which then enters the Fallopian tube. In woman this process of ovulation probably occurs about every four weeks. The ovum takes three days to reach the uterus.

After ovulation a glandular structure, the **corpus luteum**, develops in the cavity of the ruptured follicle. The corpus luteum is formed by the ingrowth of the cells of the membrana granulosa and theca interna into the antrum. These cells hypertrophy and globules of yellow pigment and lipides make their appearance in them. Strands of cells and blood-vessels grow in from the theca interna and divide the lateral cells into columns. The centre of the corpus luteum is often occupied by a clot formed from blood, liberated when the follicle is ruptured, and from the remains of the liquor folliculi which did not escape. The corpus luteum

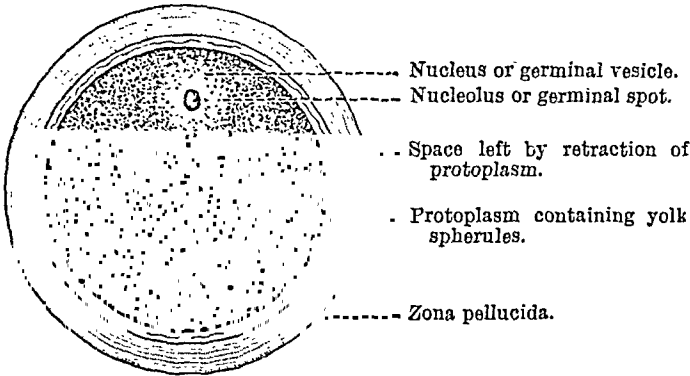


FIG. 288.—A human ovum. (Cadiat.)

begins to degenerate after a short time and always before the next ovulation, if pregnancy does not supervene. It persists when fertilisation is effected, and only atrophies shortly before the child is born. The following table gives the chief facts in the life-history of the two types of the ordinary human corpus luteum:—

	Ordinary Corpus Luteum.	Corpus Luteum of Pregnancy.
<i>At the end of three weeks.</i>	Three-quarters of an inch in diameter; central clot reddish; convoluted wall pale.	Larger; convoluted wall bright yellow; clot still reddish.
<i>One month .</i>	Smaller; convoluted wall bright yellow; clot still reddish.	
<i>Two months .</i>	Reduced to the condition of an insignificant cicatrix.	Seven-eighths of an inch in dia- meter; convoluted wall bright yellow; clot decolorised.
<i>Six months .</i>	Absent.	Still as large as at end of second month; clot fibrinous; convo- luted wall paler.
<i>Nine months .</i>		One half an inch in diameter; central clot converted into a radiating cicatrix; the external wall tolerably thick and con- voluted, but without any bright yellow colour.

The ovarian ovum or primary oöcyte (fig. 288) is a large spheroidal cell surrounded by a transparent striated membrane called the *zona pellucida*, or *zona striata*. The protoplasm is filled with large fatty and albuminous granules (*yolk spherules*), except in the part around the nucleus, which is comparatively free from them. It contains a nucleus, and usually one very well-marked nucleolus. The nucleus and nucleolus are still often called by their old names, *germinal vesicle* and *germinal spot* respectively. An attraction sphere, not shown in the figure, is also present, and a fine membrane, the *vitelline membrane*, immediately invests the protoplasm within the *zona pellucida*.

The Fallopian Tubes or tubæ uterinæ which lead to the uterus have externally a serous coat from the peritoneum, then a muscular coat (longitudinal fibres outside, circular inside), and most internally a vascular mucous membrane thrown into longitudinal folds, and covered with ciliated epithelium.

The Uterus consists of three similar layers. The muscular coat is, however, very thick, and is made up of two strata imperfectly separated by connective tissue and blood-vessels. Of these the thinner outer layer is the true muscular coat, the fibres of which are arranged partly longitudinally, partly circularly. The inner layer is very thick. Its fibres run chiefly in a circular direction; the extremities of the uterine glands extend into its internal surface. It is in fact a much hypertrophied muscularis mucosæ. The mucous membrane is thick and consists of a corium of soft connective tissue, lined with ciliated epithelium; this is continued down into long tubular glands which have, as a rule, a convoluted course. In the cervix the glands are racemose. Near the os uteri the epithelium becomes stratified; stratified epithelium also lines the vagina.

THE FORMATION OF THE GAMETES.

The production of ova by the ovary is known as *oögenesis*. The formation of spermatozoa by the testis is known as *spermatogenesis*. The prodigality of nature in providing for the continuance of the species is well illustrated by the fact that at birth the human ovary contains about 70,000 immature oöcytes. Only a minority of these attain maturity, and get situated in Graafian follicles: many follicles, moreover, never burst, but atrophy. On the average, one follicle ripens every four weeks, so that in the period between the onset of puberty and the menopause (fifteen to forty-five years of age) there is a possibility in the thirty intervening years of the production of about 400 ripe ova. Of these again a very small minority become fertilised. Still more is the lavishness of the provision illustrated in spermatogenesis; it has been calculated that in the semen ejaculated at an act of coitus there are more than two hundred million spermatozoa, and only one of these is needed for the fertilisation of an ovum.

Spermatogenesis.—The germ cells divide into spermatogonia which undergo several divisions, two of which are shown in the diagram (fig. 289). Each spermatogonium grows and becomes a primary spermatocyte; it divides into two secondary spermatocytes, and ultimately into two spermatids which develop

into spermatozoa. In the division of the primary into the secondary spermatocytes, the mitosis is heterotypic and the number of chromosomes is reduced to half the normal somatic number. This phenomenon is paralleled in the history of the oöcyte, and it will be convenient to postpone the histological details until we come to the oöcyte.

The result is that the secondary spermatocyte and its descendants, the spermatids and spermatozoa, have only half the number of chromosomes characteristic of the species. The maturing of the spermatozoa takes place within the seminiferous tubes.

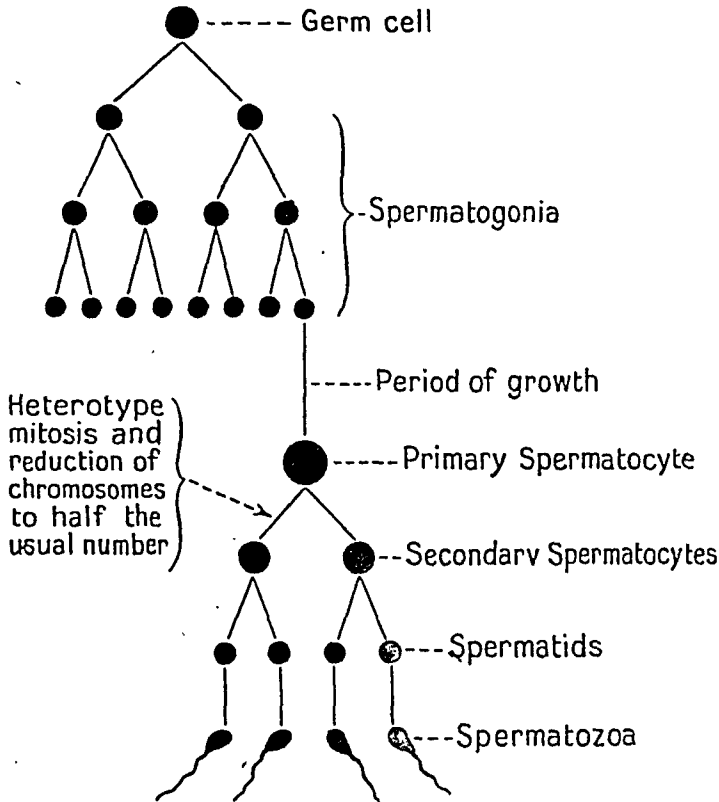


FIG. 289.—Diagram to illustrate spermatogenesis.

Oögenesis takes place on the same general lines as spermatogenesis, but with important differences in detail. In the first place, the changes in the ovary are correlated with certain changes in the uterus which result in menstruation. A second important difference is that maturation of the ovum occurs after the oöcyte has left the ovary and is on its journey along the Fallopian tube to the uterus. A third difference is that the ovum is considerably larger than the spermatozoon.

The ova arise from oögonia which are present in the ovary probably only during embryonic life. The oögonia are capable of multiplication by division. Finally each oögonium divides into two primary oöcytes which then undergo a reduction division, the first maturation division, which results in the production of the first polar body. The reduction division is characterised by a clumping together of the chromosomes at one stage, known as synapsis, and by the subsequent reappearance and pairing of the individual chromosomes. These preliminary changes are completed in the oöcytes of the human ovary shortly after birth. The subsequent stages of the division do not take place until the oöcyte is about to be ejected from the ripe follicle at ovulation.

At maturation a spindle is formed and one chromosome of each pair goes to each pole. The spindle is eccentric in position and projects, in a small protuberance of protoplasm, from the surface of the oöcyte. The division causes the separation of the little protuberance, the first polar body, from the oöcyte. This reduction division results in half the chromosomes being extruded with the first polar body and half being retained in the oöcyte, which is now known as a secondary oöcyte. The process of reduction in the female is very similar to that in the male, where it results in the formation of two secondary spermatocytes from

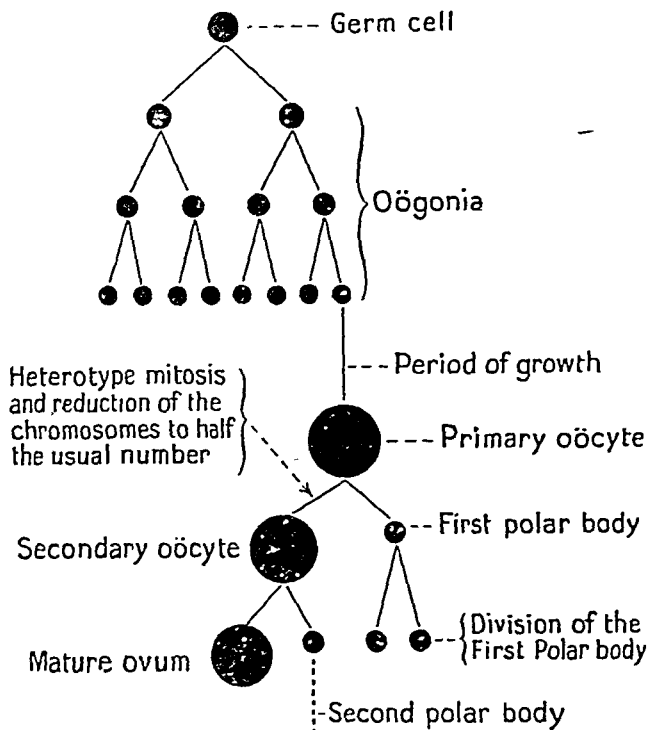


FIG. 290.—Diagram to illustrate oögenesis.

a primary spermatocyte. In both sexes the number of chromosomes in the daughter-cells is half that of the parent-cells. After the secondary oöcyte is ovulated, another division occurs, resulting in the production of a second polar body. This division does not reduce the number of chromosomes, as each is split in two in the normal manner. Simultaneously, the first polar body divides into two. The resulting three polar bodies remain in the zona pellucida, of the now mature ovum, and degenerate.

The meaning of the polar bodies has been the subject of much speculation; it is supposed that the female cell casts out certain constituents in order to make room for the addition to it of material from another individual, namely, the male. Some animals multiply without the intervention of the male sex, or the intervention occurs at long intervals with many intermediate generations; this is known as *parthenogenesis*. One must therefore suppose that the female cell has within it a male component which can be transmitted to future generations.

The ovum after it is liberated from the ovary by the rupture of a Graafian follicle, enters the Fallopian tube, the cilia of which are the main instruments for the transportation, and finally reaches the uterus. During this journey, which probably occupies some days, it becomes mature, it is fertilised, and some of the early steps in further development may also occur.

INTERNAL SECRETIONS OF TESTIS AND OVARY.

In addition to producing spermatozoa and ova the testes and ovaries elaborate internal secretions which are liberated into the blood stream.

Testis.

The principal evidence that the testis forms an internal secretion is derived from the study of effects of castration, or cases in which the testes have atrophied or become diseased. Normally in males at **puberty**, about the age of fourteen to sixteen years, there occur a series of changes which are associated with sexual maturity and the development of spermatozoa in the testes. In man a growth of hair appears on the pubis and on the face, the voice deepens, and the features become more characteristically male. In animals these secondary sexual characteristics are often associated with striking changes, such as the growth of characteristic horns or plumage. If the operation of castration is performed before puberty, the reproductive apparatus which is left (vesiculæ seminales and prostate, but not the penis) atrophies; the secondary sexual characters do not develop; the voice does "not break," the body remains sexually infantile, but never assumes female characters. In bygone days the operation was practised to provide choir singers and eunuchs to attend harems. The body, however, grows, and in some cases there is overgrowth of the skeletal and adipose tissues. Advantage is taken of this fact: *e.g.* the castration of cocks to provide table birds (capons). In eunuchs the legs often grow unusually long.

In animals there is corroborative evidence of the same nature. Thus in the cock castration arrests the development of the comb and spurs; in the stag antlers; growth is arrested in horned cattle where both sexes have horns, their growth is not inhibited by castration, though their shape may be affected. In Herdwick sheep, where the males are horned and the females hornless, the presence of the testes is essential, not merely for the initiation but also for the continuance of horn growth. Castration stops horn growth at every stage of development. (Marshall.) The operation is practised extensively on bulls, rams, and horses not needed for breeding purposes, as they become more docile.

Ligature of the ductus deferens leads to atrophy of the seminiferous tubules, whilst the interstitial cells are not affected, or hypertrophy (Steinach), and the secondary sexual characters develop as usual. It is because of this that most investigators agree that the interstitial cells of the testis are the source of the internal secretion. These cells have all the appearances of secreting cells and their full development coincides with the first appearance of

spermatogenesis. Transplantation of a testis to an abnormal position in the body cavity of a castrated animal is followed by development of the secondary sexual characters. This experiment was first done by grafts by Berthold as long ago as 1849, but subsequently extracts were substituted and it was discovered that the extracts of different

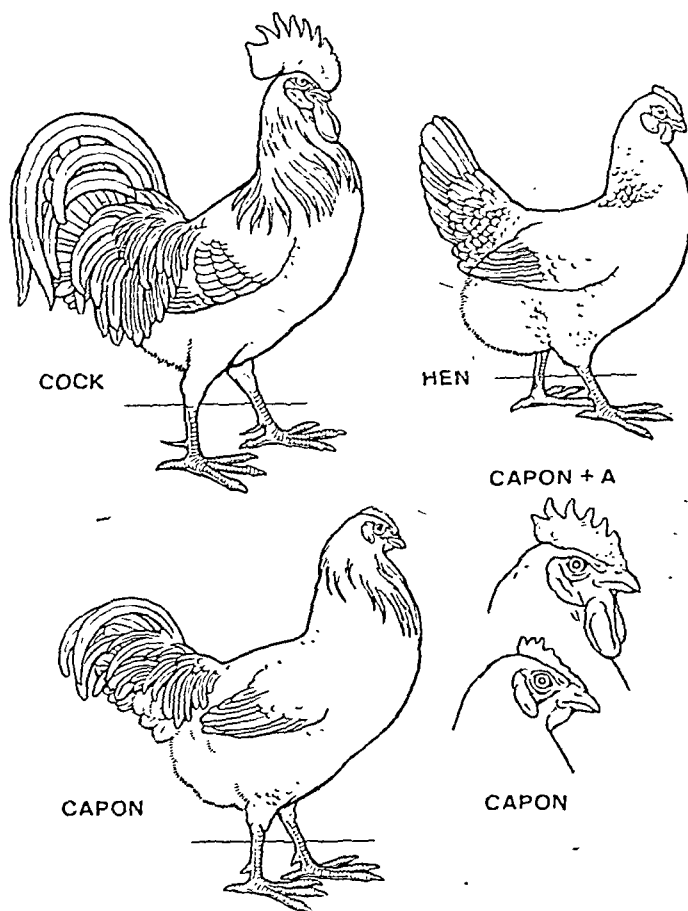


FIG. 201.—Illustration of the secondary sex characteristics in birds. The effect of castration (capon) and the administration of androgen is shown.

animals were interchangeable. It is evident, therefore, that the internal secretion acts chemically on the parts concerned and not through the intermediation of the nervous system.

The male sex hormone of the testis, now called **testosterone**, has been obtained in crystalline forms as an oxyketone having the empirical formula $C_{19}H_{28}O_2$, and its strength has been standardised according to its power of promoting comb, wattle and ear lobe growth in castrated fowls and its power of stimulating the growth

of the seminal vesicles. More recently a more convenient colorimetric method has been devised for estimating it.

Testosterone prevents also the degenerative changes which take place in the seminal vesicles and epididymis after castration. If a young animal is castrated, the injection of testosterone leads to the normal development of the sexual organs and sometimes exaggeration of the secondary sexual characteristics. The animal becomes fiercer and more dominant and sometimes there is an increased growth of the muscles. Testosterone has been used with advantage in undeveloped boys with undescended testis.

There have now been obtained from various sources a number of other masculinising substances known as *androgens*, which have the power of promoting the growth of the secondary sexual characteristics. They appear in boys about the age of ten.

Several similar substances may also be extracted not only from male urine but also from female urine, and in cases of tumour of the adrenal cortex this may be increased thirty-fold. It is possible to extract from the ovary comb-growth promoting substances and oestrogenic substances from the testis. By grafting ovaries into castrated males such as drakes and guinea-pigs it is possible to alter their secondary sexual characteristics into those of the female, who is then treated as such by males. The mammary glands secrete milk and the penis degenerates in males so treated.

These facts indicate how little is the difference between masculinity and femininity and that the production of ova or spermatozoa depends on whether male or female sex hormones predominate. This in turn depends on the possession by the sperms of the appropriate X or Y chromosome which depends on inheritance.

The activities of the testis both in regard to spermatogenesis and internal secretion are controlled by the anterior lobe of the pituitary body. Extracts of this body hasten both sexual maturity and the development of the internal secretion, while removal has the opposite effect. There is, however, also a kind of reverse reaction, for castration leads to an overgrowth of the basophil cells of the pituitary and the appearance of the so-called castration cells, *i.e.*, basophils with a signet-ring shape, while the injection of male hormone brings about a return to normal.

The Prostate.—The function of Cowper's glands and the glands of the prostate is probably to add to the semen, and to cleanse the urethra from urine prior to ejaculation; the first fluid to come out certainly contains no spermatozoa. Its contents may be squeezed out by the passage of hard fæces.

Rejuvenation.—In 1889 Brown-Séquard, a neurologist of Paris, claimed to have rejuvenated himself by extracts of testis. This

was the first time a ductless gland was ever used therapeutically. Later Voronoff made similar claims from the injection of "monkey gland" (testis).

The possible psychological effects in man have not, however, been adequately excluded, and unprejudiced observers have failed to confirm the claim that merino sheep so treated retain the fine quality of wool characteristic of young animals. It has been suggested by Steinach that the tying of the spermatic cord might promote rejuvenation by causing the acinal cells to degenerate and thus allowing the cells of internal secretion more room to grow.

Ovary.

In the human female, sexual maturity or puberty is attained about the age of thirteen or fifteen and is characterised by growth of pubic hair, the occurrence of menstruation, and a growth of the mammary glands, but few other changes. After puberty ovariectomy, a common operation because of disease, causes a cessation of menstruation and typical atrophic changes in the uterus with slight atrophy of the breasts and external genital organs. Sometimes there are metabolic changes as at the menopause (see p. 818). In the lower animals certain cyclic changes also occur and their study has shed much light on what occurs in women.

The Œstrous Cycle.

It had long been known that the occurrence of the periodic changes in the reproductive organs of female animals is dependent on the presence of the ovaries and our knowledge of the subject was much clarified by the work of Heape and of Marshall in Cambridge. Most female animals will only receive the male during a definite period in the reproductive cycle known as *œstrus* or "heat." Careful investigation of this period in the smaller laboratory animals, such as the mouse, rat and guinea-pig, has revealed a series of well recognised stages which give opportunity for putting the sex hormones on a convenient experimental basis. The *pro-œstrus*, lasting eighteen hours in the mouse, is characterised by a generalised congestion of the uterus and vagina with some bleeding, while a smear taken from the vagina shows nucleated epithelial cells. In *œstrus* proper there is still more congestion but the vagina is almost dry, while a smear now shows keratinised cells which have been lining the vagina. They are like the superficial cells of the skin, flat, non-nucleated and stain with eosin. This stage lasts forty-two hours and thereafter all the congestive changes subside into a period of rest or *diœstrus* of two or three days in the mouse in which the smear shows only leucocytes. Since the subsidence of *œstrus* is

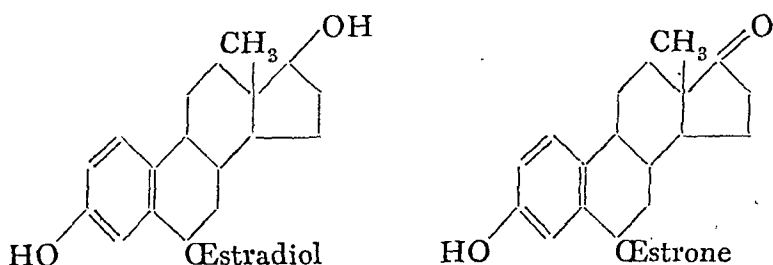
associated with and apparently dependent on the corpus luteum, this is known as the luteal phase.

Extracts of the ovary have been prepared which when injected into ovariectomised animals produce all the changes of "heat" and the term **œstrogens** has been given to the œstrus-producing substances generally. Of these a pure crystalline substance has now been isolated and is known as *œstradiol*.

That the substance is not produced by the Graafian follicles is shown by the fact that after all the follicles in the ovaries have been destroyed by X-rays, mice have a regular cycle, (Parkes). It seems probable then that the hormone is produced by the interstitial cells.

The main obstacle to the correct interpretation of the mechanism involved in the control of the reproductive cycle is that œstrogenic substances can be extracted from many other tissues and body fluids, especially the urine, where they appear as slightly altered excretion products. For instance, the richest source of material is provided by the urine of the stallion. Highly active material can also be prepared from the urine of pregnant women (*œstrone* and *œstriol*) and from the placenta.

Chemically, the œstrogens are related to the sterols but the substances found in the urine are weaker than those found in the ovary and testis. (See also Cholesterol.)



They may be standardised by finding the minimum dose which will produce an artificial œstrus in the ovariectomised mouse.

Ovarian grafts produce similar effects in the castrated animal and in humans. They may for a time also produce ova, but the grafts usually degenerate after about a year.

By grafting testis into ovariectomised females such as ducks and guinea-pigs, it has been found possible to cause them to develop the secondary sexual characteristics of the male. The injection of testosterone into the female monkey inhibits maturation and luteinisation of the follicles and suppresses the menses (Zuckermann). A conversion (known as virilism) sometimes occurs in women from overgrowth of the adrenal cortex.

The Action of Œstrogens.*—The effects of removal of the ovaries and a study of the effects of the injection of extracts into different animals indicates that œstrogens are concerned with the promotion of sexual maturity in the female and that they have a definite function in relation to pregnancy. Œstrus represents probably the préparation of the uterus for the reception of a fertilised ovum, but the final adaptation is brought about by the corpus luteum acting upon an œstro-sensitised uterus. Experimentally, Nicol has shown that a deposition of fat takes place in that part of the uterus to which the fertilised ovum is usually attached.

Œstrogens also increase the movements of the uterus, and this together with their apparently increased production towards the end of pregnancy in many animals has suggested that they may play a part in determining the onset of labour. It has been found possible to cause the expulsion of a live foetus from an œstro-sensitised uterus with oxytocin from the pituitary. This has not, however, been found possible in human subjects, but the sensitising effect is easily shown experimentally on animals. (Bell.)

The œstrogens have, however, an effect on the higher monkeys and women. They cause congestion and proliferation of various parts of the uterus-muscle, epithelium and glands, but there are no pro-œstrus changes although there is bleeding when the administration is *stopped*. There may be breast enlargement. When given to ovariectomised women, œstrogens cause a return of the uterus to its normal condition, but actual menstruation does not occur.

The action of the œstrogens is not confined to the female. In the male it causes prostatic enlargement while the female elements of the male, such as the uterus masculinus, enlarge. The cock's comb shrinks and female plumage appears. (See Parkes.)

The Corpus Luteum.—We have already seen that this structure increases in size if pregnancy ensues, and it is now known that the corpus luteum forms a hormone responsible for hypertrophic changes in the uterus and mammary glands necessary for embedding of the ovum and nourishment of the foetus.

Thus in the rabbit and ferret, in which ovulation only occurs as a consequence of coitus, the growth of the corpora lutea is associated with uterine and mammary growth, although the animals are prevented from becoming pregnant by the employment of sterilised males (Ancel and Bouin). In such cases the uterine mucous membrane undergoes vascular and glandular changes similar to those occurring in pregnancy, and at the same time the mammary glands develop to an extent sufficient to admit of the secretion of milk. This

* Most of the experiments have been made with ovarian extracts which owe their activity to œstradiol.

condition is called "pseudo-pregnancy." In all these animals the corpus luteum of pseudo-pregnancy persists for nearly as long as that of pregnancy. On the other hand, in man, and in some other mammals, where the periods recur frequently, the corpus luteum persists only for a short time if pregnancy does not supervene after ovulation.

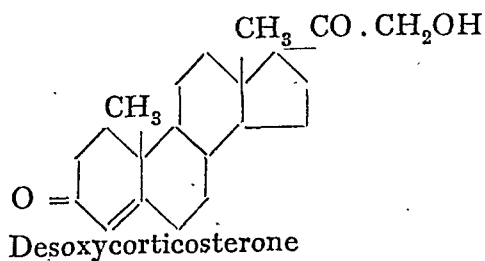
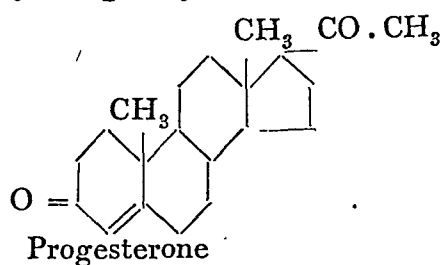
The growth of the corpus luteum is necessary for the continuance of normal pregnancy, for this comes to an end if the ovaries are removed unless luteal extract is given. Since even a mechanical stimulation of the uterus by a glass bead will, during a pseudo-pregnancy, cause the development of a decidua it may be concluded that the corpus luteum is concerned with the formation of the placenta, which in turn stimulates luteinisation. (Ashdell.)

The evidence is complete also that the corpus luteum plays a considerable part in preparing the mammary glands for lactation, but does so only with the co-operation of œstrogen and the prolactin of the pituitary—and later by a hormone of the placenta.

Some workers recognise the existence of a separate hormone, **relaxin**, which softens the pelvic ligaments after treatment with œstrogen. The corpus luteum regresses towards the end of pregnancy.

Progesterone is the name given to an active principle which has been extracted from the corpus luteum and many such substances have been synthetised or extracted from other sources. The cessation of its administration after œstrogen brings about a typical breakdown of the uterine mucosa and bleeding. It makes possible also the continuance of pregnancy even after removal of the ovaries. Its injection prevents normal ovulation, reduces the muscular activity of the uterus and prepares the mammary glands for lactation. Generally progesterone is antagonistic to œstrin, of which about 675 rat units were antagonised by 3 of progesterone. Provided the uterus is present progesterone is excreted as pregnandiol glucuronate in the urine.

Progesterone is a sterol closely related to the corticosterone of the adrenal cortex as its formula indicates. It is stated to be physiologically interchangeable.



It may be given by the mouth or injected intramuscularly.

The rabbit unit of progesterone is the amount needed to produce in the uterine mucous membrane changes similar to early pregnancy when the female has its ovaries removed soon after coitus. In this animal, as we have already said, ovulation occurs at coitus.

The Pituitary Control of the Gonads.

From what has been said in relation to diseases of the pituitary body it is evident that there is an intimate relationship between this organ and the gonads. The subject was placed on an experimental basis when Evans and Long observed that the injection of anterior extract caused an enormous increase in the number of the corpora lutea, thus showing increased ovulation. Later Smith and Engle also Zondek and Aschheim independently showed that the administration of anterior lobe tissue into immature rats resulted in precocious œstrus, marked ovarian follicular development and super-ovulation, while Corner and others demonstrated that pituitary administration produced mammary activity in rabbits.

It has now been possible to extract from the pituitary body two distinct substances, one follicle-stimulating and the other luteinising. The former is found in the water-soluble fraction of pyridine extracts and in acid extracts, the latter in the insoluble fraction and in alkaline extracts. The **follicle-stimulating hormone** causes rapid growth of the Graafian follicles and many ova are produced and discharged. It acts also on immature ovaries. The **luteinising hormone** will act on mature ovaries but not on immature ovaries unless they have received follicular stimulation. It hastens the formation of the corpora lutea from unripe follicles.

The urine of pregnant women if injected into mice or rabbits produces a luteinising effect and this is the basis of the Aschheim-Zondek test for pregnancy. There is, however, evidence that the immediate source of the hormone is in part at least derived from the placenta. It is increased in placental tumours.

In practice the blood spots due to hæmorrhage into the ovarian stroma which takes place at the same time as maturation of the follicle and luteinisation are taken as evidence of reaction. Rabbits may also be used or *Xenopus*, the South African clawed-toad (Hogben and Bellerby). In the horse the gonadotropic hormones are present in the pituitary body but they are absent from the human, it may be, because they are so freely secreted.

The anterior lobe of the pituitary also produces the substance *prolactin*, which is partly responsible for lactation.

It now appears probable that the pituitary activity is closely related to and may be responsible for sexual desire. It has been

shown that if the anterior lobe of the pituitary is removed coitus does not produce ovulation or the other changes which occur in the rabbit. It is also known that complete removal of the uterus and ovaries in women does not obliterate sexual desire.

THE INTER-RELATIONSHIP OF THE SEX HORMONES

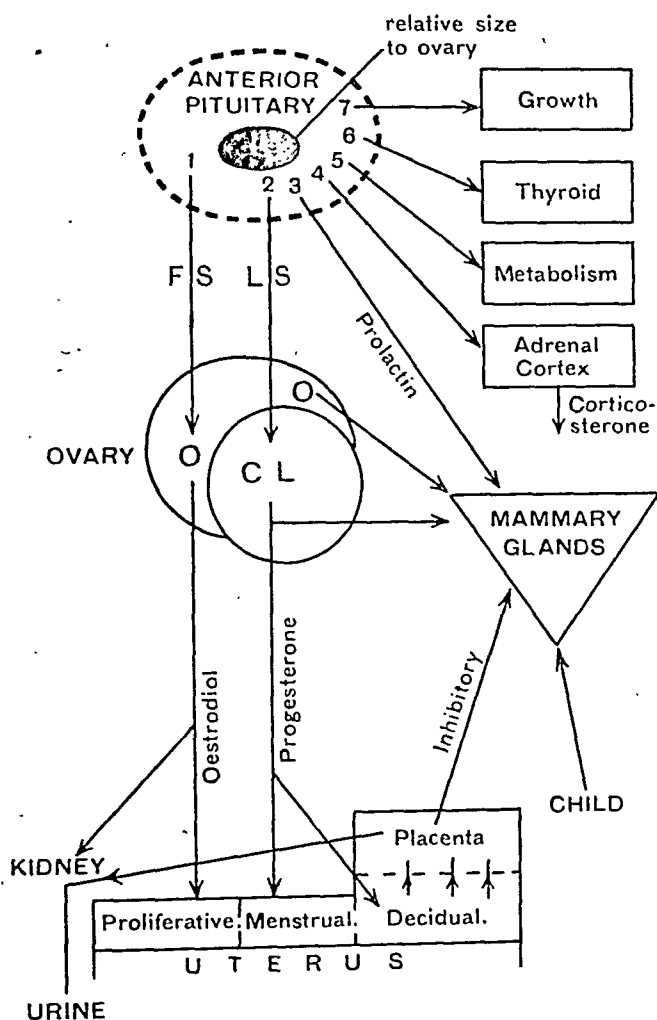


FIG. 292.—F S, follicle-stimulating; L S, luteinising; O, oestrodial; C L, progesterone. (After Secker.)

The pituitary also controls the activity of the testis. The injection of anterior lobe extracts hastens sexual maturity while removal of the pituitary leads to complete loss of sexual activity. These changes are also seen in disease of the pituitary.

A diagrammatic summary of the various activities of the pituitary body in relation to reproduction is indicated by the above figure.

LACTATION AND MAMMARY GLANDS.

When a mammal is born it is at first dependent for nourishment on a supply of milk from the mammary glands. These glands, which are of the typical compound racemose variety, pass through a series of changes during the sexual life of the female.

Before puberty they are rudimentary but thereafter develop small groups of alveoli in abundant fat and connective tissue, and remain in this state in the virgin. These changes are believed to be due to the ovarian hormones since atrophy occurs after castration in monkeys, while œstrin prevents the atrophy and causes growth in the immature animal. Without progesterone the growth, however, is incomplete.

If, however, pregnancy occurs they undergo a remarkable increase in size. The gland ducts bud out and new alveoli are produced. The cells of the alveoli elongate towards the lumen, their nuclei divide and in the part nearest the lumen fat globules appear. Later this part of the cells containing a nucleus with the fat and other substances, disintegrates to form milk in the alveoli. During this period the nipples become thickened and more prominent, their surroundings more dusky, and it may be possible to squeeze milk from them, especially when the pregnancy is near its end. The first milk or colostrum is especially rich in fat and contains the colostrum corpuscles which are probably epithelial cells from the ducts or alveoli. The proof that those changes are due to chemical substances transmitted by the blood is seen by their occurrence even in a graft transplanted to another part of the body and deprived of its nerve supply.

After lactation there is a return to a resting state in which the fat globules in the cells and the milk in the alveoli are absent, but most of the gland cells and ducts remain, while the nipple and the surrounding areola remain pigmented. The pigment appears partly to be the result of the mechanical irritation of sucking.

At the menopause the mammary glands undergo atrophy, the alveolar tissue is replaced by fibrous tissue, fat is lost and the mammæ lose their fullness.

The Control of Lactation.

As we have seen, the growth of the mammary glands at puberty is brought about by the action of œstrogen, but in pregnancy the anterior lobe of the pituitary appears to be responsible for the production of the milk; but even in the absence of the ovaries, pituitary injections will bring about the secretion

of milk in rabbits (Grueter and Stricker; Corner), while removal of the pituitary causes its suppression (Riddle). The hormone responsible appears to be distinct from the other pituitary hormones and is known as *prolactin*. These experiments in lower animals are applicable to man, for it has been found that the milk flow of women is increased by prolactin, while in pathological overgrowth of the pituitary milk secretion has been known to continue for five years.

It would seem that the placenta, in virtue of the oestrogens it secretes, eventually takes over control, for its removal with the foetus before the normal end of pregnancy at once causes a regression of the glands. Removal of the ovaries has not this effect.

Once the child is born, lactation is maintained by the sucking which may act directly or stimulate the production of prolactin. Certainly lactation may be maintained indefinitely by this means, but it ceases if a subsequent pregnancy supervenes, and this is the usual cause of the shortage in winter of milk from cows, which go dry usually about six weeks before calving.* This suggests, too, that there may be some factor present which inhibits the actual secretion of milk while the foetus is *in utero*. These would appear to be the placenta or the foetus, for milk is secreted after abortion in an advanced pregnancy, and possibly also oestrin since lactation is inhibited when it is injected.

Cessation of lactation and involution of the mammary glands occurs if the milk is not withdrawn and may be hastened by restriction of the fluid intake.

The Nervous System in Lactation.—Although, as we have seen, the primary factors in lactation are hormonal and a denervated gland can secrete milk even if transplanted, it is evident that the nervous system plays some part, for tying the ducts does not result in the involution of the gland if suckling is allowed to continue (Selye), while the secretion is negligible if the animals have been sympathectomised (Cannon). It is, however, difficult to evaluate the latter experiments as lactation may be absent or reduced for a great variety of reasons, especially in states of lowered nutrition and certain psychological disturbances.

The Amount of Milk Produced.—Modern intensive dairying has indicated that the amount of milk secreted is largely a matter of diet, both carbohydrate and protein being concerned; also, of course, water. The amount produced by a good cow on a concentrated diet of additional carbohydrate and protein with some fat, say 1000 gallons a year, could not be produced by a diet of grass alone. This would be sufficient to supply four calves,

* The duration of pregnancy in the cow is nine months.

but it is found that intensive feeding and milking cause the cows to become prematurely senile.

The Physiological Changes in Pregnancy.

It is convenient to summarise the physiological changes which occur in pregnancy as they are of considerable practical importance.

1. Menstruation ceases almost invariably.
2. The decidua develops and the uterus increases in size.
3. The anterior pituitary secretes luteal stimulating hormone and prolactin.
4. The corpus luteum develops in the ovary.
5. Œstrogenic hormones derived possibly from the anterior pituitary, ovary, and placenta are excreted and give pregnancy tests in the urine.
6. The mammary-glands enlarge and eventually produce milk, under the influence of prolactin and corpus luteum. Until birth lactation is inhibited by a hormone from the placenta. There is darkening of the mammary areola.
7. The mother tends to be depleted especially of calcium and iron, and her metabolism generally, apart from that of the child, is reduced.
8. Changes occur in the bones and ligaments of the pelvis which facilitate delivery, under the influence of a hormone of unknown origin.

Vitamins and Reproduction.—It is now clearly proved that a sufficiency of the fat-soluble vitamins A and E are necessary for reproduction (see Vitamins) and lactation. It would seem that they are intimately concerned with the nutrition of the special growth cells.

Menstruation.—In the human subject menstruation occurs, as its name suggests, usually every four weeks. The flow lasts for three to five days, and the amount of blood lost may be as much as 300 c.c. Menstruation is absent during pregnancy, and, as a rule, also during the subsequent period of lactation. It occurs in the higher primates only. In these changes in the colour of the sexual skin is also seen.

During the menstrual cycle a number of histological changes occur in the uterus, but there is wide variation in the duration of the different stages given below. (See fig. 293.)

Proliferative (6-14 days).—A few days after the endometrium or mucous membrane has been repaired it begins to thicken, while its glands increase and become tortuous.

Premenstrual or secretory (15-28 days).—The glands now fill with

mucus while the stroma cells of the rapidly thickening endometrium greatly increase in number, the capillaries dilate and fill with blood until the congested mucous membrane appears corrugated and exudes tissue fluid, often blood stained.

Destructive (3-5 days).—The endometrium now breaks down and is shed with blood, mucus and leucocytes.

Repair.—The congestion disappears and the endometrium is rebuilt.

The exact relation of menstruation to œstrus is a matter of some debate. In the lower animals ovulation accompanies œstrus,

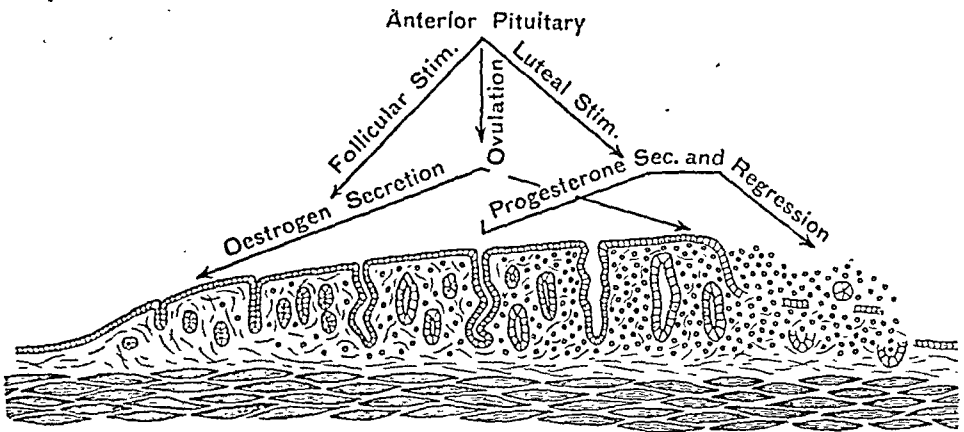


FIG 298.—Diagram (after Corner) showing the probable relationship of cyclic uterine changes to various hormones.

but observations made at operations in monkeys indicate that in higher animals and in woman it occurs midway between two menstrual periods. There is, however, evidence that ovulation may occur at other times as a response to the sexual act, as in rabbits. That menstruation corresponds to the congestive pro-œstrous stage is suggested by the fact that in the monkey the injection of œstrogen will cause menstruation; on the other hand, at puberty in the monkey ovulation definitely precedes menstruation. Since the regression of the corpus luteum corresponds in time to menstruation the latter may be looked upon as the result of this regression, the corpus luteum having been responsible for preparing the uterus for a fertilised ovum which did not appear. The unwanted endometrium is thrown off. This view conveniently explains the absence of menstruation in pregnancy, but there are many facts which do not fit into this view. A difficulty is that œstrogen will produce menstruation and that a non-ovulating monkey without a corpus luteum continues to menstruate from a resting endometrium. The factor causing this breakdown cannot be the regression of the corpus luteum, and evidence suggests that the ovaries are concerned,

for it has been found that in ovariectomised monkeys oestrogen will not cause menstruation. Since normal menstruation is associated with a marked fall in blood oestrogen, and that produced by oestrogen occurs after the injections cease, it may be suggested that it is the fall of the blood oestrogen which is most important. There is probably a cyclic mechanism causing menstruation, possibly central or possibly in the interstitial cells, just as there is in those producing ova.

The Menopause or Climacteric.

In the female there takes place, usually between the age of forty-five and fifty, a regression of sexual potentiality. The menstrual periods stop suddenly or gradually, the cessation being sometimes preceded by excessive menstruation, the glandular tissue of the mammary glands degenerates and is replaced by fibrous tissue or fat, while in some there is a degeneration of the sexual organs. Sexual desire, which is apparently a pituitary function since it persists after complete removal of the ovaries and uterus, may persist. The ovaries, however, cease to produce ova or corpora lutea and reproduction is no longer possible.

General changes often occur. There may be a gross exaggeration of the "middle-aged spread" or weight may be lost. Various psychic changes, notably depression and irritability, also occur and are successfully treated by the administration of oestrogens which make "the change of life" less abrupt. Vitamin E has also been found of great benefit especially for the vasomotor disturbance which occurs at the menopause. The beneficial effect of pituitary hormones in cases of Simmonds' disease suggests that the climacteric may be due to basic pituitary changes.

GENERAL REFERENCES TO SEX HORMONES.—Allen, 1931; Hamblin, 1939.

FERTILISATION.

Fertilisation is the union of the male and female gametes, that is to say, of the spermatozoon and the mature ovum.

The act of *coitus* or copulation is associated in both sexes with much psychological excitement, and with the phenomenon of erection. The spermatozoa are thus deposited at the entrance of the uterus, and by means of the flagellar movement of their tails they make their way against the stream of ciliary movement into the Fallopian tubes, where they are found in a living condition for many days. It is here that they meet the mature ovum and occasionally the ovum becomes embedded in the wall of a tube. Normally in man it passes down to the uterus. Fertilisation or

impregnation only requires the entrance of one spermatozoon into the ovum. - The spermatozoon pierces the zona pellucida, and the head, neck, and possibly part of the body enter the substance of the ovum, where they undergo transformation, and are converted into a male pronucleus which fuses with the female pronucleus to complete the process of fertilisation.

Loeb suggested that the action of the spermatozoon is essentially chemical, because in certain animals (for instance sea-urchins) he was able to produce artificial parthenogenesis by purely chemical methods. When the ova of the sea-urchin are placed in dilute acetic or formic acid, a membrane is formed upon the surface of the egg-cell as it is in normal fertilisation; if the ova are then transferred to concentrated sea water for a short time and then placed in ordinary sea water, they segment and produce normal larvæ. He considered that the spermatozoon brings with it enzymes or other chemical substances which excite the ovum in the same way as the chemical reagents mentioned. Such artificial fertilisation has now been carried out in frogs' eggs.

The changes by which the fertilised ovum is transformed into the young animal may take place either inside or outside the body of the parent. If they take place inside the parent, as in mammals, including the human subject, the ovum is small, and the nutriment necessary for its growth and development is derived from the surrounding tissues and fluids of the mother. If the development takes place outside the parent's body, as in birds, the egg is larger; it contains a large amount of nutritive material called the yolk, and it may, in addition, be surrounded by sheaths of nutritive substance. Thus, in the hen's egg, the yellow part alone is comparable with the mammalian ovum, and the larger part of that is merely nutritive substance. Upon the yolk is a whitish speck, the cicatricula, which is a small mass of protoplasm, about $\frac{1}{6}$ of an inch in diameter. In the cicatricula lies the nucleus or germinal vesicle, and it is this small mass of protoplasmic substance which divides and grows to produce the chick; the yolk and the surrounding white are used as food.

Ova such as the hen's, in which only a small part, the cicatricula, divides and grows, are called meroblastic. Small ova, with little food yolk, such as the human ovum, divide completely during development, but numerous gradations occur between the two extreme types.

The further development of the individual systems of organs by which the embryonic rudiments are converted into the more fully developed condition in which they are found at birth is a subject fully treated in works on anatomy, embryology, and obstetrics, and need not be dealt with in this volume. The nutrition of the embryo and the circulation of its blood are, however, matters

of primary importance, so that it is necessary to refer to the origin of the foetal membranes, as it is by their means that nutrition is carried on.

THE DECIDUA AND THE FOETAL MEMBRANES.

When the uterus is ready for the reception of an embryo it is lined by a greatly hypertrophied mucous membrane. This is called the *decidua*, because, after the delivery of the child, a portion of it comes away from the uterus with the other membranes.

The ovum has been fertilised in the Fallopian tube, and the embryo, by the time it reaches the uterine cavity, has usually reached the stage of a morula or blastula. It rapidly eats its way into the substance of the decidua which closes over it, obliterating the opening through which it passed, and thus the embryo becomes embedded in the membrane, which thereupon becomes separable into three parts.

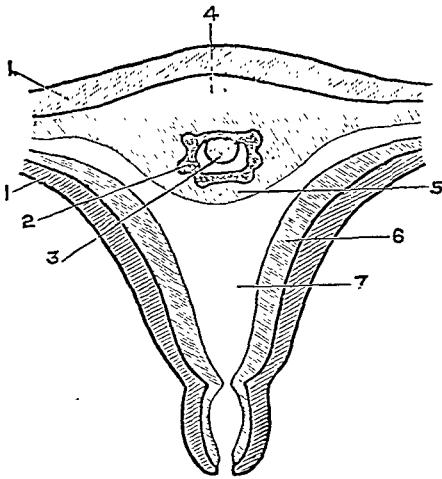


FIG. 294.—Diagram representing the relation of the developing embryo to the decidua at a very early stage. 1, Uterine muscle; 2, epiblast of embryo; 3, inner cell mass of embryo; 4, decidua basalis; 5, decidua capsularis; 6, decidua vera; 7, cavity of uterus.

1. The part between the embryo and the muscular wall of the uterus, the *decidua basalis* or *serotina*. 2. The part between the embryo and the uterine cavity, the *decidua capsularis* or *reflexa*. 3. The remaining part is called the *decidua vera*. Between the decidua capsularis and the decidua basalis lies

the embryo, which speedily becomes differentiated into the foetus and its membranes. The outermost of the foetal membranes is the chorion; this is covered with vascular villi, which dip into the decidua capsularis and basalis. Inside the chorion is the amnion, a closed sac, which surrounds the embryo and is attached to its ventral wall at the umbilicus. The amnion is filled with fluid, the *amniotic fluid* in which the foetus floats, and it forms a sheath for the umbilical cord by which after a certain time the foetus is attached to the inner surface of the chorion, or outer embryonic membrane. The umbilical cord contains not only the blood-vessels which pass between a specialised portion of the chorion which forms the foetal part of the placenta, and the foetus, but also the remains of the yolk-sac, and the duct by which it is connected with the intestine of the foetus.

As the embryo grows the decidua capsularis is expanded over its surface, and as the growth continues the uterine cavity is gradually obliterated and the decidua capsularis is forced into contact with the decidua vera, with which it fuses.

As the decidua is merely thickened mucous membrane, it naturally contains glands which become enlarged as the decidua thickens. It was believed, at one time, that the villi of the chorion entered the glands, but this is now known to be incorrect. The villi enter the interglandular substance, and, in the human subject, the glands of the decidua capsularis eventually disappear entirely. In the decidua basalis and the decidua vera the superficial portions of the glands also disappear; their deep portions remain in an almost unchanged condition, and furnish the epithelium for the regeneration of the glands and the lining of the uterine cavity after parturition. The intermediate parts of the glands in the decidua vera and the decidua basalis become very much enlarged, and form a stratum of the decidua called the spongy layer, and ultimately this layer is converted into a series of clefts, and it is along the line of these clefts that the decidua is separated at birth.

In some mammals in which the connection between the chorion and the decidua is less intimate than in the human subject, the glands persist to a greater or less extent, and secrete a fluid called uterine milk, which is absorbed by the chorion.

The portion of the decidua which undergoes the greatest change is the decidua basalis. In it a number of large blood spaces is formed, and these are separated into masses or cotyledons by fibrous strands. The cotyledons are penetrated by chorionic villi, and it is this conjunction of chorionic villi and decidua basalis which produces the placenta. The blood-vessels of the chorionic villi are usually formed by the mesodermic covering of the allantois, another foetal outgrowth. Its origin from the hind-gut is shown in fig. 295.

The **placenta** is the organ of foetal nutrition and excretion, and at full term it is seven or eight inches across and weighs nearly a

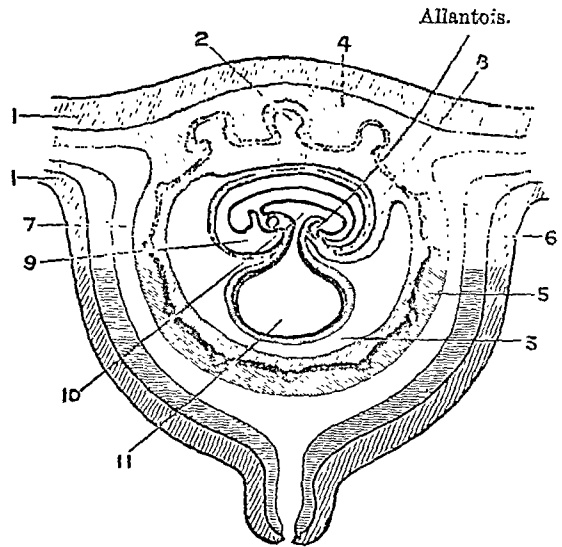


FIG. 295.—Diagram representing a later stage of development than that shown in fig. 294. 1, Uterine muscle; 2, villi of chorion of embryo; 3, coelom; 4, decidua basalis; 5, decidua capsularis; 6, decidua vera; 7, cavity of uterus; 8, bodystalk; 9, amniotic cavity; 10, primitive intestine; 11, yolk-sac.

pound. Its blood sinuses are filled with maternal blood, which is carried to them by the uterine arteries and away from them by the uterine veins. Into these blood-filled spaces the vascular foetal villi project. The foetal blood is carried to the placenta by the umbilical

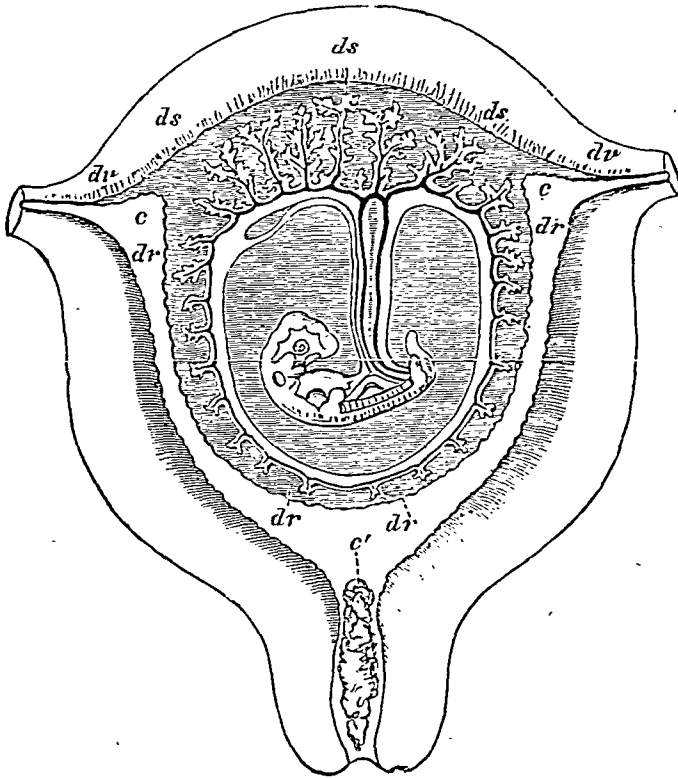


FIG. 296.—Diagrammatic view of a vertical transverse section of the uterus at the seventh or eighth week of pregnancy. *c, c'*, Cavity of uterus, which becomes the cavity of the decidua, opening at *c, c'*, the cornua, into the Fallopian tubes, and at *c'* into the cavity of the cervix, which is closed by a plug of mucus; *dv*, decidua vera; *dr*, decidua reflexa, with the sparser villi embedded in its substance; *ds*, decidua basalis or serotina, involving the more developed chorionic villi of the commencing placenta. The foetus is seen lying in the amniotic sac; passing up from the umbilicus is seen the umbilical cord and its vessels passing to their distribution in the villi of the chorion; also the pedicle of the yolk-sac, which lies in the cavity between the amnion and chorion. (Allen Thomson.)

arteries, which are the terminal branches of the aorta of the foetus; these pass to the placenta by the umbilical cord, and the blood is returned, through the cord, by the umbilical vein.

The placenta shows three markedly different stages of development, each predominating in different types of mammals, but all showing in some degree in man. (Marshall.)

1. *The Ungulate Type* have the uterine glands of the decidual portion of the placenta and secrete profuse quantities of fluid (the uterine milk of Harvey) which is absorbed by the villi of the trophoblast.

2. *The Carnivorous Type*.—Here the uterine secretion is relatively little and transient, but the decidua undergoes marked degenerative changes accompanied by autolysis. The resultant autolysate, known as embryotrophe, appears to be absorbed by the cells of the villi.

3. *The Primate Type*.—In this case the degenerative changes are very pronounced and the foetal blood is separated from the maternal by only the capillary epithelium and traces of the cytotrophoblast. Nutrition is by diffusion direct from the foetal to the maternal blood. At full term the placenta is a partially degenerated and a necrotic organ.

The functions of the placenta are:—

(a) *Nutritive*.—As outlined above.

(b) *Secretory*.—As indicated on p. 815, there is now evidence that the placenta is concerned in the elaboration of a hormone which is somehow concerned with the nutrition of the foetus, but how is by no means clear. It presumably plays some part in activating luteinisation.

During pregnancy this secretion is excreted in the urine and is presumably responsible for the gonadotropic content of this urine. With the removal of the placenta at birth the hormone is absent.

(c) *Excretory*.—Waste products of foetal metabolism pass into the maternal blood (as well as appearing in the allantoic and amniotic fluids).

(d) *Storage*.—At a period about half-way to two-thirds through pregnancy the placenta attains its maximum development. It then contains (mainly in the decidual portion) fat, glycogen and iron. At this stage the foetal liver is relatively small and contains little glycogen and fat. With the later development of the liver, this "hepatic function" of the placenta becomes reduced.

(e) *Respiration*.—Oxygen and carbon dioxide traverse the placenta by diffusion dependent on pressure difference on the

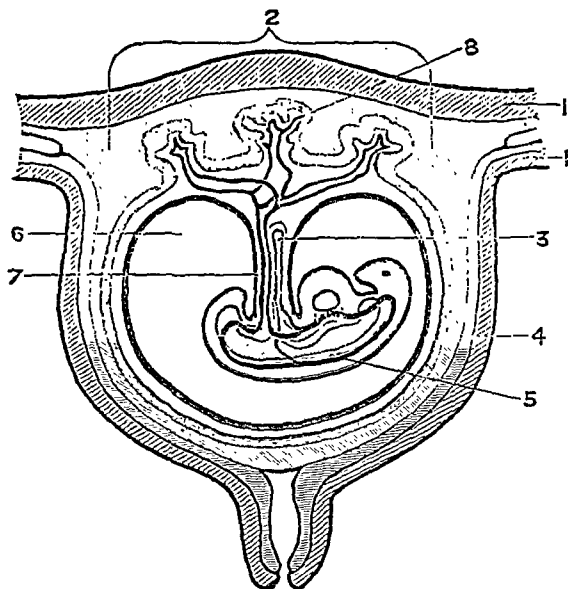


FIG. 297.—Diagram representing a later stage of development of membranes and placenta than that shown in fig. 295. 1, uterine muscle; 2, placenta; 3, yolk-sac; 4, fused decidua vera and capsularis; 5, primitive blood-vessel of embryo; 6, amniotic cavity (outer surface of amnion is fused with inner surface of chorion); 7, umbilical cord; 8, foetal villus in placenta.

two sides of the membrane. Viruses but not certain colloids, *e.g.* pyrrol-blue, also traverse it.

The *amniotic fluid* consists of water containing small quantities of protein, urea, and salts. It is an exudation from the foetal and the maternal blood, and the urea in it comes from the foetal urine which is poured into the amniotic cavity in the later part of pregnancy. Its function is mainly mechanical; it supports the

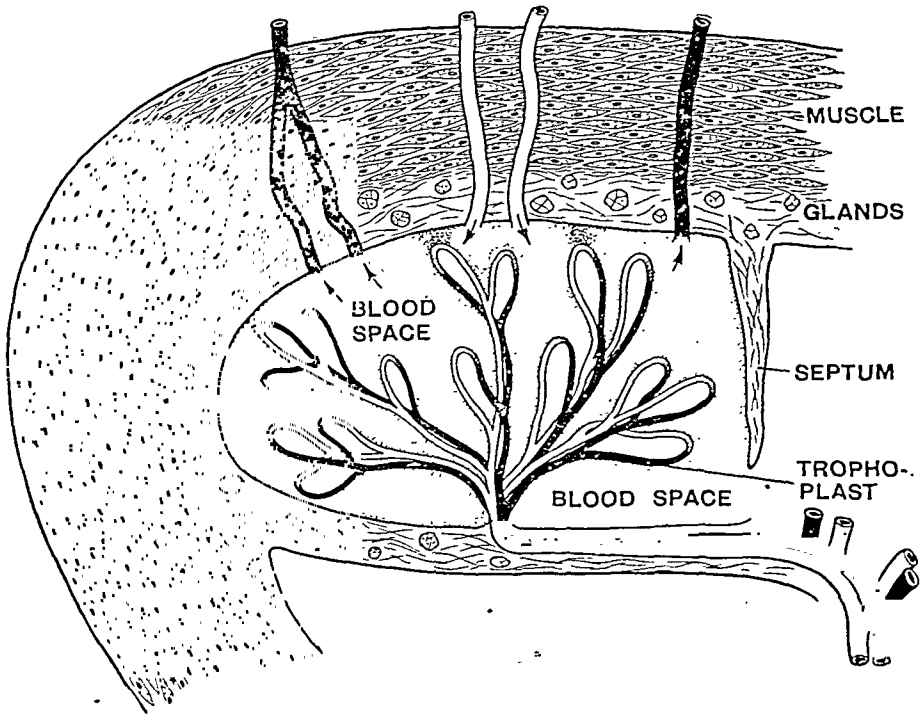


FIG. 298.—Diagram of the primate placenta.

embryo on all sides, and protects it from blows, other injuries to the abdomen of the mother, and from sudden irregular contractions of the abdominal walls.

If a pregnant animal is injected with pyrrol-blue (which is normally taken up by the reticulo-endothelial system) the appearance and behaviour of the placenta are most striking; the blue colour disappears from the skin and is concentrated in the uterus, and in time the latter, forming a centre of attraction for the dye, ultimately dispossesses all the remaining tissues of their blue. In the uterus it is in the free cells of the decidua basalis that the stain is mainly found. In quite early stages the stained cells penetrate into the primitive placenta and cast off their stained granules, which are snatched up by foetal cells in the way nutritive material

is. But when once the placenta has attained maturity, the dye is found only in the foetal cells which form the layer which separates the maternal and foetal tissues. The foetus itself remains perfectly colourless, the stain not being able to penetrate this protective barrier. Further research has shown another important point, for the same cells which vigorously absorb the stain store also glycogen, fat, and hæmoglobin temporarily before these substances pass into the foetal circulation. The avidity of such cells for the dye is thus connected with their functional activity in relation to really nutritive material; the importance of vital staining in embryological research is therefore apparent. (Huggett.)

THE FŒTAL CIRCULATION.

We shall not enter into the complex manner in which the heart and blood-vessels of the foetus develop from the embryonic rudiments; but when these are fully formed the circulation of the blood is found to differ considerably from that which occurs after birth. It will be convenient to begin its description by tracing the course of the blood, which, after being carried to the placenta by the two umbilical arteries, has returned, oxygenated and replenished, to the foetus by the umbilical vein.

It is at first conveyed to the under surface of the liver, and there the stream is divided—a part of the blood passing straight on to the inferior vena cava, through a venous canal called the *ductus venosus*, while the remainder passes into the portal vein, and reaches the inferior vena cava after circulating through the liver. Whether, however, by the direct route through the ductus venosus or by the roundabout way through the liver—all the blood which is returned from the placenta by the umbilical vein reaches the inferior vena cava at last, and is carried by it (together with the blood from the lower part of the body and lower limbs) to the right auricle of the heart, into which cavity is also pouring the blood that has circulated in the head and neck and arms, and has been brought to the auricle by the superior vena cava. It might be naturally expected that the two streams of blood would be mingled in the right auricle, but such is not the case, or only to a slight extent. The blood from the superior vena cava—the less oxygenated fluid of the two—passes almost exclusively into the right ventricle, through the auriculo-ventricular opening, just as it does in the adult; while the blood of the inferior vena cava is directed by the fold of the lining membrane of the heart, called the *Eustachian valve*, through the foramen ovale into the left auricle, whence it passes into the left ventricle, out of this into the aorta, and thence to all the body, but chiefly the head and neck. The blood of the superior vena cava, which, as before said, passes into the

right ventricle, is sent out from there in *small amount* through the pulmonary artery to the lungs, and thence to the left auricle, by the pulmonary veins, as in the adult. The greater part, however, does not go to the lungs, but instead passes through a canal, the *ductus arteriosus*, leading from the pulmonary artery into the aorta just below

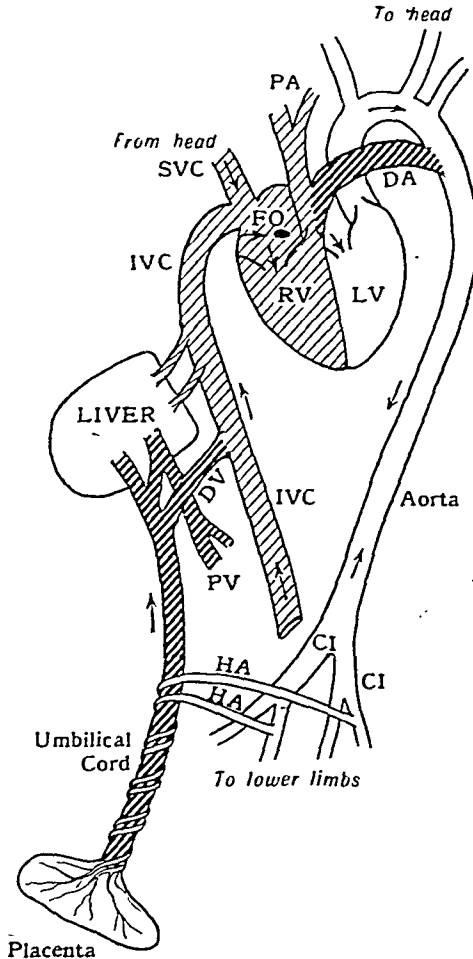


FIG. 299.—Diagram of the fetal circulation. With the exception of the portal vein, P.V., the dark shaded vessels are peculiar to the fetus and disappear in the adult.

the origin of the three great vessels which supply the upper parts of the body; and there meeting that part of the blood of the inferior vena cava which has not gone into these large vessels, it is distributed with it to the trunk and other parts—a portion passing out by way of the two umbilical *arteries* to the placenta. From the placenta it is returned by the umbilical *vein* to the under surface of the liver, from which the circulation started.

The Respiration and Nourishment of the Fœtus.

The subject of the respiration of the fœtus has been studied especially by Barcroft and Huggett and the following points appear clear:—

1. The transference of gases to and from the fœtus is by diffusion.
2. The dissociation curve of the fœtus is shifted to the left and upwards, whereas that of the pregnant animal is shifted to the right and downwards compared with the non-pregnant animal. The latter shift is due to decreased pH while the former is due to a different type of hæmoglobin as is indicated by the different shape of the dissociation curve. These changes in the fœtal and maternal blood result in a higher saturation of fœtal hæmoglobin at relatively low oxygen pressures than would otherwise occur.

It is evident that the fœtus receives all its nourishment from the mother through the placenta. It is presumed that the substances necessary, glucose, amino-acids, salts, and the like, pass through the walls of the blood-vessels of the villi by a process of diffusion.

It has been found that the blood of the fœtus differs somewhat from that of the mother, especially in regard to the variety of hæmoglobin it possesses. The fœtal hæmoglobin is capable of becoming saturated at a lower partial pressure than that of the mother. This obviously facilitates the loading of oxygen which is made particularly readily available by the fact that the blood loses alkalinity during the second half of pregnancy. Thus the pressure head of oxygen in the placenta is increased, the decreased alkalinity having a similar effect to the addition of carbon dioxide.

PARTURITION.

During pregnancy the uterus and its contents increase in size, and we have already alluded to the changes in its mucous membrane or decidua, and the formation of the placenta; the principal factor in the distension of the uterus is the accumulation of the amniotic fluid. The muscular wall of the uterus also hypertrophies; this is in part due to the formation of new muscle-fibres, and in part to the increase in size of the pre-existing muscle-fibres. The muscular wall is one of immense strength.

The fœtus "comes to term" in the human subject on the tenth menstrual epoch after conception; this averages 280 days after the last menstruation. Delivery is the result of uterine contractions or "labour pains"; the liquor amnii is thus forced downward and presses the membrane formed by the fused amnion and chorion through the cervix of the uterus which is gradually

distended. When the distension is sufficient the membrane ruptures, and the amniotic fluid escapes. The orifice is then fully distended, and the foetal head enters the pelvis, the pains become more frequent and energetic, and the voluntary muscles of the abdomen are brought into play, so that ultimately the new-born child is expelled to the exterior. The process usually lasts some hours, but the time is much prolonged (ten, twenty, or even more hours) in the birth of a first child. The child is still connected with the placenta by the umbilical cord, which is about 20 inches long, and this connection should not be severed for a few minutes in order that as much blood as possible may be aspirated from the foetal part of the placenta into the child as breathing commences.

After the child is expelled, the contractions of the uterine walls recommence after a lapse of twenty to thirty minutes, and the placenta is separated and forced out. The separation extends through the decidua along the line of the stratum spongiosum, and the fused chorion, amnion and decidua turned inside out, follow the placenta to which they are attached, constituting, with the placenta, the after-birth.

After the umbilical cord is tied and separated, the umbilical arteries inside the child become filled with blood-clot, and are ultimately converted into fibrous cords, the so-called obliterated hypogastric arteries; at the same time the allantois is also converted into a fibrous strand, the urachus, which extends from the apex of the bladder to the umbilicus.

The hæmorrhage from the uterus which accompanies and follows the after-birth may be profuse at first, but under normal conditions is soon checked by the firm contraction of the uterine walls.

Although it has been shown that delivery may occur when all nerves connecting the uterus with the central nervous system are cut through, the contractions of the organ are normally influenced reflexly through the nervous system. Stimulation of various sensory nerves will produce contractions of the pregnant uterus, and premature delivery may occur as the result of mental and physical disturbances.

The determining factor which produces the labour pains at a particular date has been much discussed; some think it is maternal in origin, such as a degenerative condition set up in the placenta or decidua, whereas others consider that the initial impulse comes from the foetus, which secretes certain products that stimulate uterine contraction.

After delivery, the uterus undergoes reduction in size at a fairly rapid rate. This has been attributed to fatty degeneration but for this there is little evidence. The theory at present most in vogue to explain "involution of the uterus" is that the process is one of autolysis due to the action of intracellular digestive enzymes. While it is occurring, the urine of the mother contains creatine, a substance which is normally absent from that excretion. It has been

supposed that this substance originates from the rapid destruction of the uterine muscle. It has, however, been shown that creatine occurs after delivery even if the uterus is amputated, so that the creatine of the uterine muscle cannot then be the source of the urinary creatine; there is evidence that the creatine is associated in some way with the metabolism of the mammary gland.

The atrophy or involution of the uterus which occurs at the menopause appears also to be produced in the same way, and it has been suggested with some reason, that the symptoms exhibited at that period of life may be in part explained as due to the absorption of the products of the autolysis of the uterine tissue.

CHAPTER LIX

THE GROWTH AND REPAIR OF THE BODY

THE growth of the body is dependent on the growth of the individual cells of which it is composed and in which the power of growth appears to be inherent. This power of the individual cells to grow, which is particularly well seen in embryonic tissues, can be shown by keeping the cells under suitable conditions. The medium commonly employed is sterilised Ringer's solution or blood-plasma + embryo extract. By this means of **tissue culture** the cells of various organs may be kept alive for an indefinite number of years. The cells, however, grow into a mass, and are liable to die after a few days. In order to continue the growth of the cells it is necessary to transplant small pieces of the culture to a new medium from time to time.

Local Growth.—Normally in the body the cells not only grow but appear to be influenced by other cells in their vicinity. The exact mechanism which prevents the different varieties of cells from invading each other is not known, and this is a fundamental difficulty in the understanding of cancer, the great characteristic of which is such invasion.

The phenomenon of general body growth is exhibited in all young mammals for a limited period which, in man, lasts until the twentieth or twenty-fifth year. At the end of this period the bones reach their normal maximum size, and the individual may be considered to have reached adult life. Thereafter, however, the power of growth is not lost, but continues to be exhibited by tissues especially if they are injured or if there is an increased demand for their activity. Thus, for example, a broken bone will repair itself, disease in one kidney will result in an enlargement of the other, or the muscles may still grow in accordance with requirements. Normally, it appears that every tissue of the body is constantly being renewed. We are all familiar with the continuous growth of the hair and the nails.

The continuance of the power of repair is of the utmost importance to the individual, since its cessation marks the onset of senility and lessened power to resist disease or recover from injury.

The growth of the body as a whole is determined largely by

heredity, but it is now realised that various factors play a considerable part. Of these the most important is the diet.

Diet in Relation to Growth.—In order that an animal should grow it is essential that it should be supplied with adequate food, not only to supply its immediate needs in regard to tissue repair and energy exchanges, **calories**, but in addition that it should have sufficient to provide for the building up of new tissue. Thus a growing boy may require as much food as a man. In relation to Protein Metabolism we have already seen that certain **amino-acids** are more essential than others in the synthesis of tissues. It has been shown, for example, that a diet lacking in lysin and tryptophan, although it will maintain life, is insufficient for growth. In addition, certain vital elements, which we designate **vitamins**, and which can only be obtained from natural foodstuffs, must be supplied if body growth and its maintenance are to be normal. Specially concerned in growth are vitamins A, D and B, while **salts**, such as those of iron, calcium, iodine, are essential. Vitamin C appears to be specially important in repair after injury, especially for the activity of the fibroblasts which produce fibrous tissue.

Certain ductless glands also play an important part in growth. The **thyroid**, we have seen, is specially concerned in the metabolic rate and metamorphosis of cells. The anterior lobe of the **pituitary** is also intimately concerned with growth, especially that of the skeleton, and if over-active may lead to gigantism.

THE SKELETON.

This is the framework on which the soft parts are built. It consists of the bones and cartilages which are bound together by ligaments of fibrous tissue.

Cartilage.

Serving a similar supporting function in the body as bone, cartilage is popularly known as gristle.

In some regions, as at the ends of bones, the cartilage is *hyaline* and has a simple structure. No blood-vessels penetrate the matrix, through which lymph simply soaks to reach the cartilage cells. This relatively poor nutrition furnishes a possible reason why hyaline cartilage in many situations (costal, laryngeal, tracheal) shows a tendency to become calcified late in life.

On boiling, the ground-substance of cartilage yields a material called *chondrin*. This resembles gelatin very closely, and the differences in its reactions are due to the fact that chondrin is really a mixture of gelatin with varying amounts of mucoid substances.

Cartilage of this kind forms the rib cartilages and prefigures most bones in development.

In some regions where toughness is required, as in the semilunar cartilages of the knee-joint or the intervertebral discs, the cartilage cells lie in a dense fibrous matrix. This variety is known as **white fibro-cartilage**.

In others where flexibility is desirable, elastic fibres are scattered between the cells. Such **yellow or elastic fibro-cartilage** is found in the pinna of the external ear and the epiglottis.

Development of Cartilage.—Like other connective tissues, cartilage originates from mesoderm; the cells are unbranched, and the disposition of the cells in fully formed cartilage in groups of two, four, etc., is due to the fact that each group has originated from the division of a single cell, first into two, each of these again into two, and so on. This process of cell division is accompanied by the usual karyokinetic changes.

Each cell deposits on its exterior a sheath or capsule; on division each of the daughter-cells deposits a new capsule within this, and the process may be repeated.

Bone.

Bone is composed of organic and inorganic constituents which are so intimately blended and incorporated the one with the other, that it is only by severe measures, as for instance by a white heat in one case and by the action of concentrated acids in the other, that they can be separated. Their close union, too, is further shown by the fact that when by acids the inorganic matter is dissolved out, or on the other hand when the organic part is burnt out, the shape of the bone is alike preserved.

The proportion of organic matter is greater in the bones of infants than in those of adults.

To the naked eye there appear two kinds of structure in different bones, and in different parts of the same bone, namely, the *dense* or *compact*, and the *spongy* or *cancellous* tissue. Thus, in making a longitudinal section of a long bone, as the humerus or femur, the articular extremities are found capped on their surface by a thin shell of compact bone, while their interior is made up of the spongy or cancellous tissue. The *shaft*, on the other hand, is formed almost entirely of a thick layer of the compact bone, and this surrounds a central canal, the *medullary* cavity—so called from its containing the *medulla* or marrow.

In the flat bones, as the parietal bone or the scapula, the cancellous structure (diploë) lies between two layers of the compact tissue, and in the short and irregular bones, as those of the wrist

and foot, the cancellous tissue fills the interior, while a thin shell of compact bone forms the outside.

Marrow.—There are two distinct varieties of marrow—the *red* and the *yellow*.

Red marrow occupies the spaces in the cancellous tissue; it is highly vascular, and thus maintains the nutrition of the spongy bone, the interstices of which it fills. It contains a few fat-cells and a large number of *marrow-cells*. The marrow-cells are amœboid, and resemble large leucocytes; the granules of some of these cells stain readily with acid and neutral dyes, but a considerable number have coarse granules which stain readily with basic dyes such as methylene blue. Among the cells are some smaller nucleated cells of the same tint as coloured blood-corpuscles. These are termed *erythroblasts*. From them the coloured corpuscles of the blood are developed. There are also a few large cells with many nuclei, termed *giant-cells* or *myeloplaxes*.

Yellow marrow fills the medullary cavity of long bones, and consists chiefly of fat-cells with numerous blood-vessels; many of its cells also are the colourless marrow-cells just mentioned.

Periosteum.—The surfaces of bones, except the part covered with articular cartilage, are clothed by a tough, fibrous membrane, the *periosteum*.

Histology of Bone.

Examined with a rather high power, bone substance is found to contain a multitude of small irregular spaces, approximately fusiform in shape, called **lacunæ**, with very minute canals or *canaliculi* leading from them, and anastomosing with similar little prolongations from other lacunæ (fig. 300). In life the lacunæ and canaliculi are occupied by bone-cells which are essentially connective-tissue cells; these form the organic matrix of the bone in which calcium becomes deposited. The nutrient lymph passes from place to place by way of the canaliculi. In very thin layers of bone, as in cancellous bone, only lacunæ may be visible; but on making a transverse section of the compact tissue as of a long bone, *e.g.* the humerus or ulna, the arrangement shown in fig. 300 can be seen.

The bone is mapped out into small circular districts, at or about the centre of each of which is a hole, around which is an appearance as of concentric layers; the *lacunæ* and *canaliculi* follow the same concentric plan of distribution around the small hole in the centre, with which indeed they communicate.

On making a longitudinal section, the central holes are found to be simply the cut extremities of small canals which run lengthwise through the bone, anastomosing with each other by lateral branches

(fig. 300); these Haversian canals are occupied by blood-vessels and nerves.

Lamellæ and Fibres of Compact Bone.—In the shaft of a long bone three distinct sets of lamellæ can be clearly recognised.

1. *Circumferential* lamellæ; these are concentrically arranged just beneath the periosteum, and round the medullary cavity.

2. *Haversian* lamellæ; these are concentrically arranged round the Haversian canals to the number of six to eighteen round each.

3. *Interstitial* lamellæ; these connect the systems of Haversian lamellæ, filling the spaces between them they consequently attain their greatest development where the Haversian systems are few, and *vice versa*.

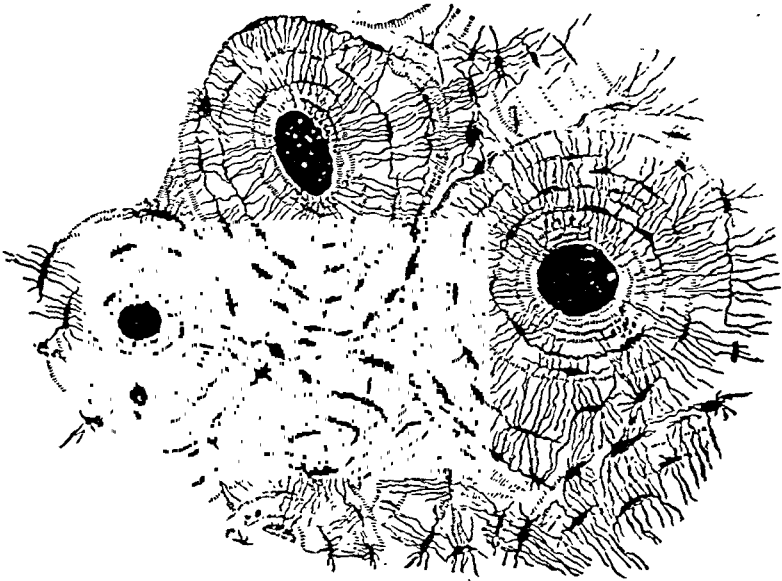


FIG. 300.—Transverse section of compact bony tissue (of humerus). Three of the Haversian canals are seen, with their concentric rings; also the lacunæ, with the canaliculi extending from them across the direction of the lamellæ. The Haversian apertures were filled with air and debris in grinding down the section, and therefore appear black in the figure, which represents the object as viewed with transmitted light. The Haversian systems are so closely packed in this section that scarcely any *interstitial* lamellæ are visible. $\times 150$. (Sharpey.)

The lamellæ are permeated by very delicate fibrils running in bundles through the calcified matrix. All the fibres in a lamella are parallel, but in adjacent lamellæ the fibres usually run in different directions. They correspond to the white fibres of connective tissue and form the source of the gelatin obtained by boiling bone.

The outer layer of a bone is pierced by relatively thick tapering fibres called the *perforating fibres of Sharpey*, resembling in character the ordinary white or more rarely the elastic fibres. These perforating fibres are really ingrowing processes of the periosteum (fig. 303).

Nourishment of Bone.

From the blood-vessels of the periosteum branches enter the little foramina on the surface of the bone, and find their way to the Haversian canals, described above. The long bones are supplied also by one or more nutrient arteries which, entering the shaft so as to reach the medullary cavity, break up into branches for the supply of the marrow, from which again small vessels are distributed to Haversian canals from the interior of the bone. Other small blood-vessels pierce the articular extremities for the supply of the cancellous tissue. The bone-cells in the lacunæ are nourished by lymph which gains access to them by the canaliculi.



FIG. 301.—Longitudinal section from the human ulna, showing Haversian canals, lacunæ, and canaliculi. (Rollett.)

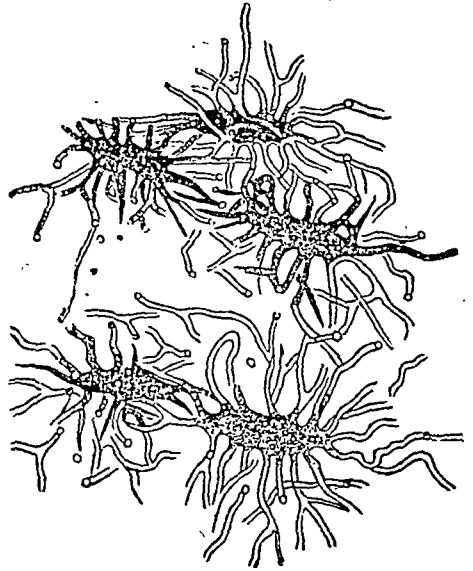


FIG. 302.—Bone-corpuscles with their processes as seen in a thin section of human bone. (Rollett.)

Development of Bone.

From the point of view of their development, bones may be subdivided into two classes:—

(a) Those which are ossified directly in the embryonic connective tissue—*e.g.*, the bones forming the vault of the skull, parietal, frontal, and a certain portion of the occipital bone.

(b) Those whose form, previous to ossification, is laid down in *hyaline cartilage*—*e.g.*, humerus, femur.

In both cases, bone is produced by bone-formative cells called

osteoblasts. In the first mode of development the osteoblasts lay down bone directly, without any intermediary stage (ossification in *membrane*), while in the second the future bone is first modelled in cartilage upon which, after it has undergone certain changes, the osteoblasts proceed to lay down bone as round a scaffolding (ossification in *cartilage*).

Ossification in Membrane.—Where bone formation is about to occur the embryonic branched mucoid cells first multiply actively, become larger and apparently more crowded together and their processes disappear or at any rate become less obvious as the cell

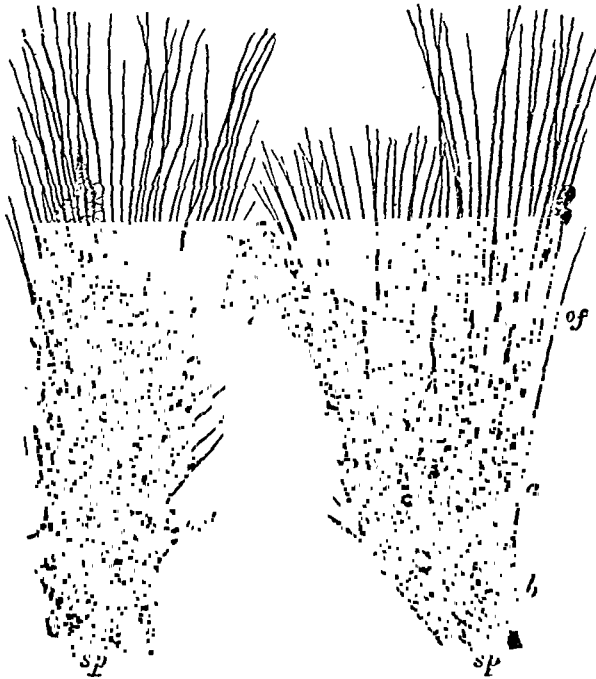


FIG. 303.—Part of the growing edge of the developing parietal bone of a fetal cat. *sp*, Bony spicules with some of the osteoblasts embedded in them, producing the lacunæ; *of*, osteogenetic fibres prolonging the spicules with osteoblasts (*ost*) between them and applied to them. (Schafer.)

bodies become more rounded. The vascularity of the area increases. At what is termed the primary centre of ossification, corresponding usually to the centre of the future bone, the altered cells, which may now be called *osteoblasts*, proceed to lay down bone between and round themselves in the ground-substance. Radiating spicules of bone grow out from the original centre, each covered by a layer of osteoblasts which produce lengthening and thickening of the spicule. Some of the osteoblasts become buried in the bony tissue they form round themselves, becoming then bone corpuscles each in a little lacuna. Where active extension of a spicule is occurring,

it is often seen to be capped by a tuft of fibres on which the advance guard of osteoblasts is arranged. Such is called an *osteogenic tuft*, calcification occurring between the fibres under the influence of the osteoblasts, the fibres and the cells gradually become embedded within the advancing bone. The spicules or trabeculae of bone branch and anastomose with one another so that a meshwork of bone is formed. In certain situations where bony strands are being thickened, a regular row of osteoblasts is formed on their surface. In other positions a sculpturing process is at work, the newly-formed bone being demolished by large multinucleated bone-destroying cells called *osteoclasts*. This continuous remodelling goes on to accommodate the developing bone to the growth changes around it. As the skull cavity, for example, enlarges, the curved bones in the vault have fresh material added to their convex surfaces by osteoblastic action coupled with absorption of bone on their concave surfaces by osteoclastic activity. Round each individual bone the connective tissue condenses to form a fibrous sheath, the *periosteum*, beneath which are arranged the osteoblasts on those surfaces where further bone growth is taking place. The trabeculae towards the surface become altered to compact bone with typical Haversian systems, while in the interior the trabecular arrangement is retained to form the cancellous bone containing spaces filled with red marrow.

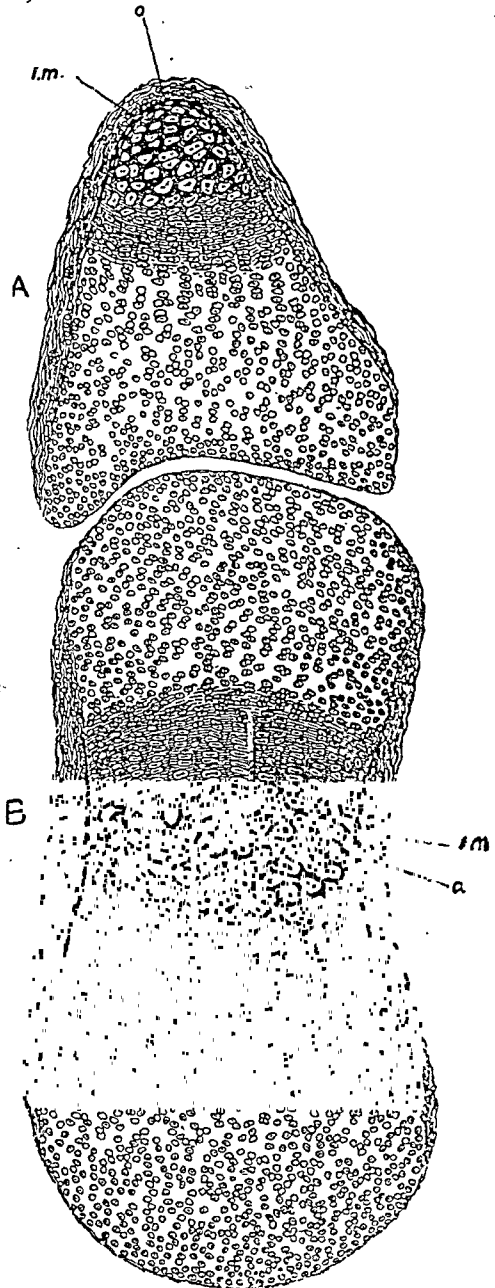


FIG. 304.—Section of two fetal phalanges; the cartilage-cells in the centre of B are enlarged and separated from one another by calcified matrix. *i.m.*, Layer of bone deposited under the periosteum; *o*, layer of osteoblasts by which this layer was formed. The rows of cartilage-cells are seen on each side of the centre of calcification. In A, the terminal phalanx, the changes begin at the tip. (After Dixey).

Ossification in Cartilage.—This process is typically seen in the development of one of the long bones of the limbs. Here the future bone is first modelled in hyaline cartilage, but it must be remembered that this foetal cartilaginous bone is many times smaller than even the medullary cavity of the shaft of the mature bone, and, therefore, that not a trace of the original cartilage can be present in the bone of the adult. Its purpose is indeed purely temporary; and, after its calcification, it is gradually and entirely absorbed. This cartilaginous model is at first completely sheathed in a condensation of the mucoid tissue termed the perichondrium. Over the articular ends of the bone this disappears later.

The process of ossification may be most conveniently described as occurring in three principal stages.

The first stage consists of two sets of changes, one in the cartilage, the other under the perichondrium. These take place side by side. In the cartilage the cells in the middle* become enlarged and separated from one another. They become arranged in rows in the direction of the extremities of the cartilaginous rod. The cartilage-cells degenerate and the thinned walls between the enlarged spaces undergo a calcareous change. Simultaneously with this, a row of osteoblasts appears beneath the perichondrium round the centre of the shaft and these proceed to form layer after layer of bone on the surface of the cartilage. The osteoblastic layer gradually advances towards the ends of the cartilage and by it the layer of bone around the middle of the shaft is extended. As the layers are formed, some of the osteoblasts get walled in between the layers and become bone-cells.

We may roughly compare the two sets of cells engaged in the process to two races of settlers in a new country. The cartilage-cells constitute one race, and so successfully build for themselves calcareous homes as to be completely boxed up; so they waste and disappear, leaving only the walls of their homes. The osteoblasts, the other race of cells under the perichondrium, are forming layers of true bone in that situation. Some, it is true, get walled-in in the process, and become bone-corpuscles, but the system of intercommunicating lacunæ and canaliculi maintains their nutrition.

These two races are working side by side, and at first do not interfere with each other. But soon comes a declaration of war, and we enter upon the *second stage* of ossification, which is very appropriately called the *stage of irruption* (fig. 305). Breaches occur in the bony wall which the osteoblasts have built like a girdle round the calcifying cartilage, and through these the osteogenic tissue is poured into the calcified cartilage. This consists of *osteoblasts*,

* This is the case in nearly all the long bones, but in the terminal phalanges the change occurs first, not in the middle but at their distal extremities.

osteoclasts, and a store of nutrient supply in the shape of blood-vessels.

Having got inside, the osteoclasts set to work to demolish the calcified homes of the cartilage-cells, and thus large spaces are formed. On the ruins of the calcified cartilage, the osteoblasts proceed to deposit true bone in layers, just as they were wont to do in their own country, under the periosteum.

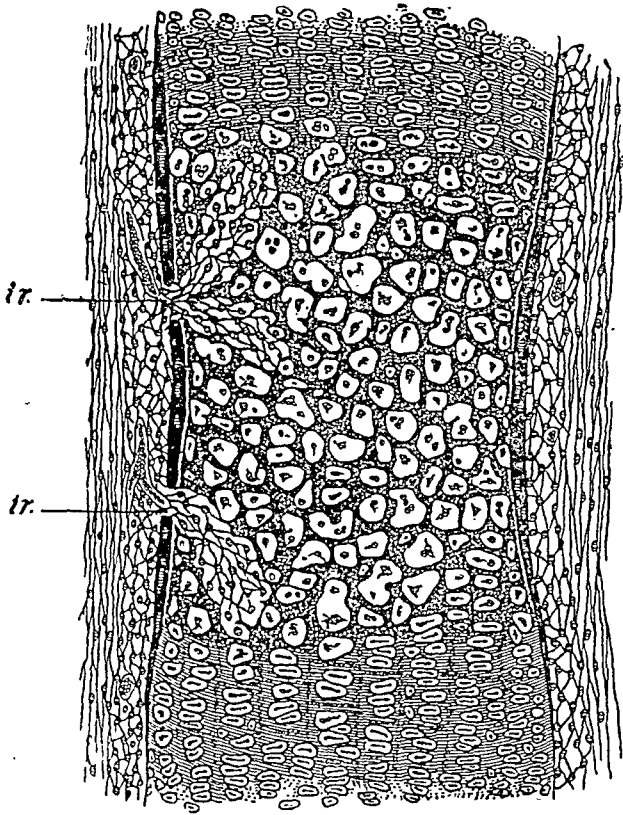


FIG. 305.—Ossification in cartilage showing stage of irruption. The shrunken cartilage-cells are seen in the primary areolæ. At *ir* an irruption of the subperiosteal tissue has penetrated the subperiosteal bony crust. (After Schafer.)

The third stage is the extension of the process of ossification, thus initiated towards the extremities of the cartilage. The cartilage-cells enlarge, form longitudinal rows, widen their spaces, and finally degenerate. Calcification occurs in the remnants of cartilaginous matrix, and on this scaffolding the osteogenic tissue extends the area of true bone, with ultimately the complete disappearance of the calcified cartilage. The first-formed bone within the shaft and the deeper layers of subperiosteal bone are absorbed by osteoclasts so that a medullary cavity is established, which continues to enlarge in all directions.

The bone which is first formed is less regularly lamellar than that of the adult. The lamellæ are not deposited till after birth and their formation is preceded by a considerable amount of absorption. To carry our simile further, the osteoblasts are not satisfied with the rough constructions that they were first able to make, but having exterminated the cartilage, they destroy (again through the agency of the giant osteoclasts) their first work, and build regular lamellæ, leaving lacunæ for the accommodation of those who desire to retire from active warfare. It is the process of osteoclasts which is stimulated by the hormone produced by the parathyroid gland to set free calcium into the blood-stream.

After a time the cartilage at the ends of the shaft begins to ossify independently to form the epiphyses. Between each epiphysis and the shaft a plate of actively-growing cartilage persists for a time (*epiphyseal plate*). But this plate does not become thicker, as ossification attacks it on both sides. Thus the bone grows in length, until towards adult life the cartilaginous plate ceases to grow and becomes obliterated by bony fusion between shaft and epiphysis.

At the same time bone grows in width by the deposition of layers under the periosteum, like successive rings formed under the bark of a growing tree. The inner layers become absorbed, however, to provide for expansion of the medullary cavity.

It must be remembered that even after growth in all directions is fully established, bone remains a living tissue containing living bone-corpuscles. If need arises, as in the repair of fractures, or in structural alterations of the bones called forth to resist new strains and stresses, the bone-corpuscles can resume their original osteoblastic and osteoclastic activities.

Chemistry of Bone.

Of the dry weight of adult bone freed from fat, two-thirds consist of inorganic matter, the remainder being mainly the protein collagen (which gives gelatin on boiling with water) and mucoids. Analyses of bones of a large variety of animals agree in assigning about 90 per cent. of the total inorganic matter of bone to calcium phosphate, the majority of the remaining 10 per cent. being calcium carbonate with magnesium phosphate. The calcium phosphate appears to be present mainly in the form of the very insoluble tertiary salt, $\text{Ca}_3(\text{PO}_4)_2$, though Bassett believes that a somewhat more basic salt, $[\text{Ca}_3(\text{PO}_4)_2]_3 \text{Ca}(\text{OH})_2$, is the main constituent. The bony structure of the adult is not absolutely permanent, and in whatever form the main constituent is present it is to be realised that this apparently quite insoluble skeleton is really in equilibrium with the blood, and under various pathological conditions (some of which are controllable) may suffer absorption or overgrowth.

Chemistry of Ossification.

For normal ossification to take place it is necessary that there should be present not only the general requirements for growth, but also an adequate amount of calcium and phosphorus, together with sunlight and vitamin D. Also since calcium and phosphorus are absorbed into the blood in solution, there must be present some mechanism by which these substances become deposited where they are required. The chemical reactions which are believed to take place are as follows:—

If a solution is saturated with a very slightly soluble solid such as calcium phosphate $\text{Ca}_3(\text{PO}_4)_2$, any addition to the dissolved Ca^{++} or PO_4''' will lead, by laws of mass action, to a precipitation of the solid. It is known that the concentrations of calcium and phosphate ions in blood plasma are such that at the *pH* of plasma these concentrations are very near the limit of saturation of that fluid with tertiary calcium phosphate. In fact, Holt, La Mer, and Chown have stated that blood is 200 per cent. supersaturated with calcium phosphate. It is clear that conditions would be very favourable for the local deposition of tertiary calcium phosphate if the concentrations of Ca^{++} or PO_4''' could be increased *at the site where deposition was necessary*. A mechanism which appears to ensure that these favourable conditions actually occur in growing bone has been demonstrated by Robison and his collaborators. The work had an accidental beginning in the observations of Robison, that during enzymotic hydrolysis of the calcium salts of hexose phosphate in the products of fermentation of yeast juice, an insoluble precipitate of calcium phosphate was formed. Experimental evidence of a very convincing kind has shown that an enzyme, *phosphatase*, a phosphoric esterase, is present in ossifying cartilage, mainly in the zone of hypertrophic cartilage cells and also beneath the periosteum in young bone (*i.e.* in the zone in which calcium salts are being actively deposited). It is also present to a lesser extent in adult bone. This enzyme will convert soluble calcium salts of phosphoric esters into insoluble calcium phosphate *in vitro*, and Kay and Robison have shown that it will hydrolyse a portion of the phosphoric esters normally occurring in circulating blood. This hydrolysis, if it takes place in the locality in which the enzyme is known to occur, will clearly lead to a local increase in inorganic phosphate concentration, *i.e.* to the conditions just mentioned as being very favourable for the local deposition of tertiary calcium phosphate. It has been found, however, that the presence of an amount of phosphorus sufficient to bring about the proper calcium phosphorus ratio is essential. The precipitation of the phosphorus

by beryllium carbonate causes a variety of rickets in spite of adequate calcium and vitamin D.

The following observations increase the likelihood that this enzyme plays an essential part in the chain of processes leading to bone formation:—

1. If a bone taken freshly from a very young animal is split lengthways and immersed in a very dilute solution of calcium glycerophosphate or calcium hexosemonophosphate in saline, calcium phosphate is deposited in the neighbourhood of the osteoblasts and hypertrophic cartilage cells. This can be demonstrated histologically, and is particularly clearly seen in rachitic bones (Robison, Shipley).

2. The enzyme is also present in teeth, particularly in growing teeth.

3. The enzyme is *not* found in such cartilage as does not normally ossify, such as that of the trachea.

4. In embryonic cartilage in the chick, or in the cartilage of the human patella which only begins to ossify some three or four years after birth, the appearance of the enzyme and the commencement of ossification are simultaneous.

5. It has recently been shown by Kay that in certain diseases (osteitis deformans and osteitis fibrosa) where there is profound disorganisation of the bones, relatively large amounts (up to twenty or more times the normal) of the phosphoric esterase occur in the plasma. In the normal individual and in most diseased conditions the amount of phosphatase in the plasma is small. Lesions of the bone involving a large part of the skeleton are thus associated with a faulty or abnormal distribution of the enzyme.

The subject of ossification is of special interest in the healing of fractures. From what has been said earlier regard to vitamin D (p. 379), it is necessary to provide adequate phosphorus, calcium, and this vitamin to promote absorption. Skimmed milk is probably the best medium for the conveyance of these.

As general growth experiments suggest, vitamin A is concerned in bone growth, but changes in the bone appear late if the vitamin is withdrawn from the diet. On the other hand excessive vitamin A causes a marked acceleration of growth.

The effect of vitamin C deficiency is also marked, but it would seem that the changes are due to a weakening of the supporting tissues.

Bone as a Store of Calcium.—In relation to the parathyroid it has been seen that the bones act as a storehouse for calcium (Kay, 1932).

DEATH.

It is not altogether inappropriate to conclude a book which deals with life by a few sentences on *Death*, which forms the final chapter for each individual. As the prime of life is past, signs of old age begin to appear—the eyes become feeble, the hair becomes grey, the cartilages calcify, the muscles become weaker, digestion gets feebler, and metabolism in every way more and more imperfect. If this continues, life is ultimately terminated by natural death, in which the functions get weaker and weaker and finally cease. Death from old age is, however, comparatively rare; the common cause of death is accident, in which term we include disease. In the activity of youth many a disease is vanquished, but as the powers of resistance diminish with increasing years, some ailment usually upsetting more particularly some important organ will ultimately find the body unable to repel its attack.

Legally, death in man is said to have occurred when the heart and respiration have stopped. Sometimes when these are both weak the exact time of death may be very difficult to decide, but it will be realised that for some time after death it would be possible to demonstrate the activity of many organs if they were removed and perfused with oxygenated blood.

IMPORTANT PHYSIOLOGICAL DATA ✓

WHICH SHOULD BE MEMORISED.

Note.—As far as possible average figures are given, but it must be understood that even normals may vary outside the limits given.

Vascular System.

Heart-rate, resting, 50 to 80 per minute.

Heart-output, resting, 4 to 6 litres per minute.

Heart-output in exercise, up to 30 litres per minute.

Blood-pressure, resting—

Systolic, 105 to 150 mm. Hg.

Diastolic, 70 to 90 mm. Hg.

Capillary, 5 to 35 mm. Hg.

Blood-flow velocity—

in main arteries, 1 metre per second.

in capillaries, 0.5 mm. per second.

Pulse-wave velocity, 6 to 7 metres per second.

Ringer's solution, NaCl 0.9 per cent.,

KCl 0.042 per cent., CaCl₂ 0.024

per cent., NaHCO₃ 0.015 per cent.

Blood volume, $\frac{1}{14}$ to $\frac{1}{14}$ body-weight, i.e. about 6 litres in adult.

Red corpuscles, 5 to 6 millions per c.mm.

White corpuscles, 5000 to 10,000; polymorphs, 70 per cent.; lymphocytes, 23 to 25 per cent.; large mononuclear, 1 per cent.; eosinophils, 2 to 3 per cent.; basophils, 0.05 per cent.

Blood pH, 7.4.

Blood sugar, 0.08 to 0.18 gm. per 100 c.c.

Blood urea, 30 to 40 mg. per 100 c.c.

Blood creatinine, 1 to 2 mg. per 100 c.c.

Blood urea nitrogen, 10 to 15 mg. per 100 c.c.

Blood calcium, 10 mg. per 100 c.c.

Non-protein nitrogen, 25 to 40 mg. per 100 c.c.

Hæmoglobin content, 14 gms. per 100 c.c.

Oxygen capacity, 17 to 20 c.c. per 100.

Respiratory System.

Atmospheric Air.

O, 20.96 per cent.

CO₂, 0.04 per cent.

Expired Air.

O, 16.4 per cent.

CO₂, 4.1 per cent.

Alveolar Air.

O, 13 to 14 per cent.

CO₂, 5 to 6 per cent.

Vital capacity, 3000 to 4000 c.c.

Tidal air, 400 to 500 c.c.

Respiratory rate, 9 to 20 per minute.

Supplemental air, 1500 c.c. approx.

Complemental air, 1500 c.c. approx.

Residual air, 1300 c.c. approx.

Oxygen in arterial blood: amount 18.5 to 19.5 c.c. per cent.; tension 80 mm. Hg.

Oxygen in venous blood: amount 13.5 c.c. per cent.; tension 50 mm. Hg.

Carbon dioxide in arterial blood: amount 54 c.c. per cent.; tension 45 mm. Hg.

Carbon dioxide in venous blood: amount 58 c.c. per cent.; tension 48 mm. Hg.

Oxygen consumption, 200-400 c.c. per minute.

Carbon dioxide output, 160-250 c.c. per minute.

Basal metabolic rate, resting, 1700 Calories per day or 40 C. per sq. m. per hour.

Total Respiratory Quotient, 0.82.

} resting.

Foods.

Calorific values per gramme and respiratory quotients—

Carbohydrates.	Fats.	Proteins.
4.1 C.	9.3	4.1 in body, 5.6 in calorimeter.
R.Q. 1.0	0.7	0.8

Milk.

	Proteins.	Fats.	Carbohydrates.
Cow (Ayrshire)	3.5	3.7	4.5
Human	1.7	3.4	6.2
			} very variable.

Gastric Contents, etc.

HCl, not usually above 0.2 per cent.

Inorganic chlorides, not usually above 0.35 per cent.

To convert HCl to chlorides multiply by $\frac{58.5}{36.5}$

Optimum pH of ptyalin, 6.7; of pepsin, 1.3; of trypsin, 8.1.

Fat in dry fæces, 25 per cent.

Urine.

Urea 1.5 to 2 per cent., daily excretion 20 to 40 grams } ratio about 50 to 1.

Ammonia, daily excretion 0.3 to 1.2 gram.

Creatinine, daily excretion 0.9 gram.

Chlorides (as NaCl), daily excretion 10 to 16 grams.

Sulphur (as SO₃), daily excretion 2 grams.

Neutral sulphur, daily excretion 0.18 gram.

Phosphates, daily excretion 2 to 4 grams.

Uric acid, daily excretion 0.5 to 0.75 gram.

Volume, 1500 (approx.); pH 5 to 8; sp. gr. 1015 to 1030.

Eye (reduced).

Distance of nodal point from cornea, 7.3 mm.

Focal length, 15.5 mm.

Length of eye, 22.8 mm.

Muscle and Nerve.

Nerve impulse rate, cold-blooded, 30 metres per second.

Nerve impulse rate, warm-blooded, 120 metres per second.

Refractory relative period of nerve, 0.015 second; absolute, 0.003.

Refractory period of muscle, 0.005 second.

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